Respiratory Diseases

Task Force Report on
Problems
Research Approaches
Needs

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The Lung Program
National Heart and Lung Institute

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FOREWORD

In its commitment to an effective balanced effort that is responsive to national health needs, the Lung Program of the National Heart and Lung Institute looks to the community of physicians and biomedical scientists for information, professional judgments and advice. It draws upon this counsel in formulating an orderly plan for a program that will lead to improved diagnosis and treatment of respiratory diseases, and, ultimately, to their prevention. On a continuing basis, such advice is provided by the Pulmonary Diseases Advisory Committee and the National Advisory Heart and Lung Council. But for intensive, indepth analysis of certain problems, the Lung Program solicits help from groups of experts who serve for a limited period to achieve a specified objective. The Task Force on Research in Respiratory Diseases is such a group.

The Lung Program recognizes that at present some respiratory diseases are not receiving an emphasis commensurate with their importance to national health. A balanced program must address a spectrum of diseases from infancy through adulthood, and an effective program must embrace a breadth of problems and research approaches. Problems addressed must range from etiology and pathogenesis to therapy and rehabilitation; research approaches must extend from biochemistry and pathology to epidemiology and clinical trials. To assist in identifying disease problems and research approaches that warrant a high priority in the Lung Program's immediate and long-range plans, the Task Force was charged to assess the magnitude of the public health problems and the current state of knowledge relative to particular respiratory diseases, and to recommend specific steps by which the present program might be strengthened and long-term goals realized.

So that the Task Force would be of workable size and have achievable responsibilities, it was necessary to limit the types of diseases to be studied. Although the report emphasizes diseases that are major health problems in the adult, many of these diseases also occur in children.

The twelve-member Task Force was initiated in October 1971 and presented its final recommendations in June 1972. Dr. Claude Lenfant, Associate Director for the Lung Program, NHLI, served as chairman of the Task Force as a whole; each of the other members served as chairman of an *ad hoc* panel of experts who, through meetings and correspondence, formulated the eleven panel reports. Task Force members and some panelists also met with an *ad hoc* Panel on Fundamental Research Approaches, which discussed how basic scientific disciplines could contribute to solutions of problems of respiratory diseases. An economist served as consultant to the Task Force as a whole and provided the appended data on the economic consequences of respiratory disease problems.

Panelists, selected by panel chairmen in consultation with the entire Task Force, were chosen to include a spectrum of opinion as well as expertise, particularly with regard to controversial areas. Thus, panel reports reflect the views of many scientists, not alone those of the panel chairmen. Each report has been reviewed by the Task Force as a whole as well as by consultants to the Task Force chairman. The latter were drawn from the biomedical community, the Pulmonary Diseases Advisory Committee, and the National Advisory Heart and Lung Council. In all, 189 biomedical scientists contributed either as Task Force members, panelists or consultants.

This report is submitted to Dr. Theodore Cooper, Director, of the National Heart and Lung Institute, who will entertain its recommendations in consultation with the Institute's Advisory Council and other advisory committees. The report identifies disparities between what is needed and what is being done in the field of respiratory diseases. It will be considered in the light of the Institute's resources, mandate and overall goals. It is disseminated to the scientific community interested in respiratory diseases in the hope that it will be a stimulus to new approaches to persisting problems of prevention, diagnosis, therapy and rehabilitation.

This report represents an effort that involved a major segment of the time of each member of the Task Force over many months. It also reflects a remarkable response from the biomedical community that contributed in various ways. The names of Task Force members, panelists and consultants are listed in the following pages. To all of these the Lung Program of the National Heart and Lung Institute acknowledges its gratitude for their invaluable help.

Bethesda, Maryland
October, 1972

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CHAIRMAN'S SUMMARY

INTRODUCTION

Diseases of the lung constitute a major national health problem of increasing dimensions. Although the Task Force did not consider all respiratory diseases, those represented in this report account in aggregate for an estimated 150,000 deaths, 60 million days lost from work, and 40 million days of bed-restricted activity each year. To this must be added costs to the economy -- more than six billion dollars annually, the psychologic impact on patients and their families, and the burden to society. Many of these diseases originate in childhood, young adulthood or the most productive middle years and are marked by recurring episodes or persisting symptoms throughout life.

Compounding the usual difficulty of obtaining reliable data on vital statistics, is the fact that many of the diseases considered by the panels are poorly recognized, hence, under-reported. On balance it is fair to say that estimates in this report are conservative and emphasize the staggering dimensions of the national toll from these diseases of the lung.

As the Task Force could not undertake to report on all respiratory diseases, it selected specific disorders or categories of diseases that constitute important public health problems. Some panels considered groups of diseases: *nonallergic diseases of the airways*, including emphysema, chronic bronchitis and bronchiectasis; and *diseases of the pulmonary vasculature*, including cor pulmonale, pulmonary hypertension, pulmonary edema and pulmonary embolism. Others focused on particular diseases that characterize a larger group; for example, asthma as an *allergic disease of the airways*, and sarcoidosis as a *noninfectious granulomatous disease*. Several panels concerned themselves with *interstitial pulmonary diseases*, especially diffuse fibrosis and acquired connective tissue disease, infectious pneumonitis and allergic pneumonitis, and granulomatous diseases. Still others addressed themselves to problems common to most respiratory diseases: *chemical structure and function of the lung*; the lung as a target for airborne insults *(environmental diseases)*; and *care of acute and chronic respiratory failure*.

Reports by the eleven panels and an appendix on economic costs highlight the magnitude of the health problems consequent to these diseases. Following assessments of the current state of knowledge, the reports summarize the most pressing unsolved problems as perceived by each panel. Finally, each panel recommends operational

steps to solve these problems. Panelists were urged to limit themselves to items of the highest priority. It should be noted that the panels' conclusions and recommendations are addressed to both immediate and long-range solutions. A balanced program to combat disease must include objectives that could have an early pay-off in terms of better health while at the same time it must explore paths to more lasting benefits, even though they take longer to achieve. The panels indicate areas in which knowledge has advanced to the point that it can be used to alleviate some aspects of human disease if ways can be found to disseminate widely what is already known, and if resources can be developed to apply this knowledge to the care of patients. In addition they look to more lasting and wider-ranging benefits through study of the mechanisms that underlie not one, but many respiratory diseases. New avenues have opened that provide insights into genetic, biochemical, immunologic and ultrastructural changes which are implicated in the pathogenesis of most respiratory diseases. To bring these to bear on problems of human disease requires new types of physical resources, specially trained manpower, and new kinds of supportive mechanisms. The panel reports suggest ways to capitalize on these promising new insights.

Although the panels worked independently and concerned themselves with different diseases, the constellation of problems they identify are common to diseases with quite different clinical manifestations. In the following synthesis these common threads are emphasized, threads that draw to a focus fundamental issues and new developments which warrant attention because they transcend the problems of any one respiratory disease. Although some promising research approaches have evolved in the context of a specific disease, their application can lead to better diagnosis, treatment or prevention of many respiratory disorders. Hence, this synthesis sacrifices details about specific diseases to spotlight problems and solutions that could have a broad impact on national health.

SYNTHESIS OF PANEL REPORTS

Until recently, respiratory diseases have been studied largely by physiologic approaches. Pulmonary physiology has contributed greatly to an understanding of clinical problems and continues to be essential to studies of natural history, diagnosis and evaluation of therapeutic regimens, as well as other facets of respiratory disease problems. It remains a vital part of the overall attack against these diseases, both through the application of what is known and the development of more refined and sensitive measures of physiologic alterations. But with the emergence of new developments at the cellular, ultrastructural and molecular level, channels have opened for innovative approaches of great promise. By capitalizing on these new approaches as well as extending those that have been productive in the past, the diagnosis, treatment, and prevention of respiratory diseases could be advanced significantly.

Therapy of pulmonary diseases has been largely palliative, but curing or preventing these diseases could be possible if:

-etiologic factors can be identified and then removed or their action blocked;

-mechanisms by which disease develops can be understood and therapies directed at critical pathogenic processes;

-diseases can be detected early in their course and treated before irreversibility develops.

These objectives are interlocking; advances in one will inevitably lead to progress toward others.

Fundamental Knowledge of Disease Processes

As emphasized by the panels, the key to understanding pathogenesis, which is in turn the key to developing treatments that are curative rather than palliative, depends upon fundamental knowledge of underlying disease processes.

Cellular, Ultrastructural and Molecular Characteristics of the Lung

A neglected area of investigation which all panels allude to is the study of cellular, submicroscopic and molecular structure and function of the lung in health and disease. While such components have been identified, their precise nature and distribution, their functional roles in the normal lung, how they are modified as a consequence of disease and how they contribute to the disease process all require study. This broad problem is the focus of one panel report and is reinforced in other reports in relation to specific diseases. For example, collagen metabolism is of great importance in diseases that result from tissue destruction or atrophy, as in emphysema, and also in diseases characterized by proliferative processes, such as pulmonary fibrosis. Other tissue components, e.g., macrophages, have an important role in the lung's defense against such insults as infectious agents and inhaled particles. Still other cells are essential to the metabolism of pharmacologic substances that control airways and vascular tone. These and other tissue elements and substrates may be involved in such major pathologic events as the respiratory distress syndromes. Real advances against the problems of respiratory diseases depend upon understanding these normal structures, their functions, and how they are modified in disease. Each panel suggests avenues of fundamental research that are likely to be fruitful for specific diseases, but these avenues are also relevant to diseases addressed by other panels.

Protective Mechanisms of the Lung

Continuously exposed to the environment, the normal lung is protected from insult by a variety of defense mechanisms. The importance of understanding normal protective mechanisms and how their failure or abnormality leads to disease is emphasized by many of the panels. At present this promising area of investigation is largely unexplored.

Not all persons exposed to the same etiologic agents necessarily develop a disease, which suggests that *genetic factors* may predispose to disease or protect from it. Genetically determined characteristics, which may be structural as well as functional, are believed to have a role in emphysema and irreversible obstructive lung disease, in asthma, connective tissue diseases, the usual hypersensitivity pneumonitis and granulomatous lung diseases. Panels concerned with these diseases point to the importance of well-controlled epidemiologic studies on host characteristics.

As emphasized with regard to asthma, hypersensitivity pneumonitis, granulomatous diseases and interstitial fibrosis, *immunologic mechanisms* have an important role in the lung's defense against injury. However, the nature of immunologic dysfunction that leads to disease, the conditions necessary to stimulate an immune response, the degree to which the response may be genetically determined, and the mechanisms by which the normal lung defends itself against antigens are poorly understood. The reports underline the complexity of investigations on the lung's immunologic mechanisms as well as their importance to development of therapeutic regimens that can correct or restore this protective reaction when it fails.

Phagocytic cells constitute a potent *cellular defense mechanism* against a variety of insults: physical and chemical as well as infectious. Depending on the nature of the insult, alveolar macrophages and other phagocytes may be the vehicle of an immune response, the source of enzymes causing lung destruction, or the source of bacteriolytic enzymes. While the mode of action of alveolar macrophages is still uncertain, their great importance is related to the high prevalence of infectious agents that cause or aggravate many, if not all, of the respiratory diseases addressed by the Task Force. Panel reports point to the need to learn the mode of action of phagocytic cells and how these actions can be controlled to prevent or treat pulmonary diseases.

Other important components of the host defense system are the *protective transport mechanisms*, which include lymph flow, mucus production and ciliary motility. Elucidation of their normal modes of action and their alteration in disease are essential to understanding problems related to pulmonary infections, pulmonary edema, respiratory distress syndromes, reversible and irreversible airway diseases, and all environmental respiratory diseases. For example, as hypersecretion of mucus occurs in most respiratory diseases, an understanding of its chemistry and how its secretion is controlled would open the possibility of modifying it pharmacologically.

Physiologic and pathophysiologic studies of the type that have contributed so richly in the past to an understanding of the clinical aspects of pulmonary function should be continued. Panels allude to the importance of such studies to clinical recognition of a disease by observations of physiologic behavior. The reports also emphasize the importance of physiologic investigations into measurable subtle changes that will make it possible to detect early the physiologic alterations, which -- if unchecked -- will lead to irreversible disease. This requires a complete knowledge of the

normal lung so that fine physiologic and pathophysiologic alterations will be recognized. For instance, an understanding of normal smooth muscle physiology, and particularly its neuropharmacologic control, is important with regard to both airway disease and pulmonary vascular diseases. Similarly, an understanding of airflow characteristics of airways and their dependent alveoli is relevant to problems of depositions of dust and submicron particles as well as to the recognition of the earliest functional impairment. But such physiologic research must be coupled with studies of biochemistry and molecular biology. For example, neuropharmacologic control of the airways is linked to metabolic processes by which the lung produces substances that modify and mediate neuropharmacologic reactions. Similarly, the transfer of gas from air to blood is affected by the condition of lung tissue, its cells and its substrates.

Etiologic Factors in Lung Diseases

Although panel reports focus on endogenous or exogenous etiologic factors with reference to a specific disease or groups of diseases, most etiologic agents are implicated in a number of respiratory diseases.

Genetic and immunologic factors appear to be the most important endogenous causes of lung diseases. They not only affect the organism's response to exogenous agents, but may themselves sometimes be modified by exogenous factors. Their importance and possible control through better knowledge of fundamental processes are discussed in the preceding section, which is addressed to this aspect of the panel reports.

Among exogenous etiologic factors, *cigarette smoking* is by far the most important. There is evidence that it may cause chronic irreversible airway disease and emphysema, and also contribute to the induction, progression and severity of allergic reversible airway disease. An aggravating effect of smoking has been suspected in infectious and hypersensitivity pneumonitis and in other syndromes resulting from air pollution or from exposure to occupational dusts and fumes. The effect of smoking is most conspicuous in patients developing chronic respiratory failure, which is the eventual complication of many respiratory diseases. On the basis of the panel reports, the conclusion is unavoidable that the problem of smoking is unique in its impact on national health. The need for specific studies addressed to this problem is emphasized by several panels. Especially important are studies designed to influence the smoking habits of the general population. However, it must be recognized that it may be impossible to eliminate smoking. Therefore, in addition to attempts to alter smoking habits by behavioral studies or to modify their effect by pharmacological agents, it is essential to investigate the cellular, molecular and functional effects of cigarette smoke to learn its mechanism of action.

The primary focus of one panel, *infectious agents* are also alluded to in one or another context by all panels. Infection by microorganisms (bacteria and viruses) can be the primary cause of a pulmonary response, or an associated factor that exacerbates an underlying disease. Some microorganisms, such as slow viruses, are difficult to recognize and probably have an insidious action. Their possible role in diseases like sarcoidosis and interstitial fibrosis is not yet fully understood. Because infections have such a marked

role in respiratory diseases, any steps toward their control would have a striking impact on national health. Since it is not possible to eliminate microorganisms from the ambient environment, panels recommend studies to control specific infectious agents and to reinforce the lung's protective mechanisms. As noted elsewhere in this report, the latter approach requires fundamental knowledge of these mechanisms.

Environmental pollutants are etiologic agents of the utmost importance. In some diseases they are primary agents, as in hypersensitivity diseases, e.g., asthma and hypersensitivity pneumonitis; and occupational diseases. In other instances, they are associated factors that contribute to the severity of disease, e.g., in infectious pneumonitis. They also undoubtedly potentiate the harmful effects of cigarette smoking. While it is unrealistic to expect to eliminate most environmental pollutants, panel reports suggest that systematic studies can diminish their impact significantly, especially if each pollutant that causes disease is recognized. This is especially important in the cases of those pollutants associated with certain industries and of organic antigens that cause hypersensitivity reactions. Investigations on the pattern of particulate deposition in the airways and lung tissue, the dose-response relationship, and the mechanisms of response to particulates are important because they seem to be common denominators for many respiratory diseases.

Recommended approaches to etiology of pulmonary diseases include epidemiologic investigations and the development of animal models, approaches that would provide clues to the action of endogenous and exogenous etiologic factors and would also shed light on important clinical problems.

Clinical Problems

Although clinical problems are specific to a disease or groups of diseases, the suggested approaches to diagnosis, prevention and therapeutic management are often common to most respiratory diseases.

Prevention and *diagnosis* are linked. If a disease can be diagnosed before it becomes irreversible, the possibility opens to interrupting its course. They are also linked conceptually, as an understanding of underlying disease mechanisms is essential to effective diagnosis as well as prevention.

Some diseases, particularly hypersensitivity diseases that are a consequence of environmental antigens, can be effectively prevented by control or removal of etiologic agents that initiate the disease process. For example, bird fanciers disease, maple bark strippers disease and certain forms of farmers lung have been cured or their progression prevented by removal of offending antigens. The potential impact of an effective antismoking effort is emphasized by the panels. Prevention might also be achieved by enhancing host protection against environmental factors; for instance, vaccines against infectious agents. But at best this is a distant possibility.

Early diagnosis, as the panels emphasize, depends upon an understanding of the underlying disease mechanisms and of the functional changes that ensue from tissue alterations. For example, the development of a specific immunologic test for diagnosis of sarcoidosis is justified by the knowledge that in this disease there is fundamental alteration of the immune mechanism.

The possibility that an abnormal immune response is involved in diffuse pulmonary fibrosis suggests a similar approach to its early diagnosis. For disorders such as emphysema and chronic bronchitis, pulmonary edema, pulmonary hypertension and pulmonary embolism, minimal physiologic and biochemical abnormalities must be recognized as a basis for technologic development of simple, reliable, noninvasive tests. Such tests would be important not only for early diagnosis, but also for serial assessments during investigations of the natural history of these diseases.

For most diseases discussed in this report, therapeutic management at present is palliative rather than curative. Although progress in palliative treatment has been made over the last few decades as a consequence of pathophysiologic studies, several panels suggest that regimens could be improved through controlled studies as well as through wider and more effective dissemination of information already available.

Emphasizing the dearth of curative treatments for respiratory diseases, the panels note that major obstacles have been lack of understanding of underlying disorders and pathogenic mechanisms, and failure to achieve early diagnosis. They suggest that if specific alterations associated with a disease were known, they could be corrected. For example, the self-perpetuating processes that lead to scarring and the factors that determine healing are not understood, but these processes might be interrupted and chronic changes in the lung prevented through application of fundamental knowledge of the underlying mechanisms. Once an allergen is known it is possible to employ specific desensitization. It might also be possible to manipulate the immune processes once the etiologic agents and basic immunologic processes are elucidated. Similarly, the alterations in collagen found in emphysema and fibrosis might be corrected if collagen metabolism were understood. And alterations in lung clearance mechanisms associated with many respiratory diseases might be controlled if mucus composition, and the mechanisms of mucus production, were defined.

The panels suggest that clinical problems related to diagnosis, prevention and treatment can best be elucidated by studies of natural history. These would serve to identify etiologic factors, develop sensitive tests to detect disease early and determine whether it is reversible, and assess the effectiveness of therapeutic regimens.

The similar scientific objectives that emerge from the panel reports point to approaches that are relevant to most diseases. These approaches include controlled studies, epidemiologic studies, investigations of natural history, and development of animal models. Some panels also allude to the need for clinical trials addressed to detection as well as treatment of diseases such as chronic respiratory failure, airway disease and pulmonary embolism.

Resources for Implementation

Of particular concern is the need for resources to achieve the panels' objectives. It is evident that special resources are required for multidisciplinary studies of the type stressed in the panel reports.

Manpower with training in both fundamental science and clinical medicine is needed. The panels emphasize that training should include disciplines which until now have not been brought to bear sufficiently on problems of lung disease; particularly, biochemistry, immunology, pharmacology, molecular biology, epidemiology, and both gross and microscopic morphology. The key issue is to train individuals so that they will use these disciplines for research on respiratory disease.

Panels concerned with acute and chronic respiratory care and the respiratory distress syndromes emphasize the need for better dissemination of available knowledge about patient care. They also stress the need for clinical personnel, both professional and paramedical, to meet the current shortage of individuals who can utilize the sophisticated techniques that have been developed for therapeutic management.

To implement programs of the types envisaged, panels recommend the development of centers. These are necessary not only for fundamental and applied multidisciplinary research programs, but also for dissemination and application of information about clinical care, and for training clinical personnel. Some panels, concerned with diseases that may not warrant development of special centers, advocate *collaborative studies* between institutions on a regional or even national basis.

MAJOR CONCLUSIONS AND RECOMMENDATIONS

Conclusions and recommendations relative to specific diseases or groups of diseases appear at the end of each panel report. Their major thrust is summarized below.

General Conclusions

1) Although it is well recognized that data on incidence, prevalence, morbidity and mortality of respiratory diseases are incomplete, these diseases clearly constitute a major national health problem whose magnitude is increasing. Taken together the respiratory diseases considered by the panels clearly constitute a major health problem both nationally and internationally, and any advance in treatment or prevention would benefit large numbers of people.

2) For these diseases, the current state of knowledge opens many promising research opportunities that are within reach and could be solved in a relatively short time. These opportunities indicate new directions but do not exclude those now being followed. Continuation of current research efforts and initiation of new scientific objectives are both necessary to reach the goals of preventing many respiratory diseases and of treating effectively those that cannot be prevented.

3) It is important to recognize that most scientific objectives are common to several groups of respiratory diseases. Any advance toward reaching these objectives will have a major impact.

The main scientific objectives identified in the reports are:

-elucidation of pathogenic processes in the lung, as a key to developing curative treatment;

-recognition of endogenous and exogenous etiologic factors, which is a key to early detection of respiratory disease and to development of more effective therapeutic regimens;

-consideration of clinical problems related to diagnosis and treatment so as to achieve early detection and prevention and to initiate early curative treatment.

4) Present resources are inadequate to realize these scientific objectives or to initiate new research directions. A new type of manpower is needed combining interests in pulmonary clinical medicine with expertise in a variety of fundamental disciplines. Advances will be best achieved through research programs that are multidisciplinary.

General Recommendations

I. Advances in the field of respiratory diseases are limited by the lack of information about the normal and diseased lung.

RESEARCH PROGRAMS, BOTH FUNDAMENTAL AND APPLIED, SHOULD BE DEVELOPED IN A CONCERTED EFFORT TO ATTAIN THE GOALS OF EFFECTIVE TREATMENT AND, ULTIMATELY, PREVENTION OF LUNG DISEASES.

FUNDAMENTAL RESEARCH PROGRAMS SHOULD BE MULTIDISCIPLINARY SO THAT THE WEALTH OF AVAILABLE INFORMATION FROM BASIC SCIENTIFIC DISCIPLINES WILL BE BROUGHT TO BEAR ON LUNG DISEASES.

PROGRAMS SHOULD BE DIRECTED TO THE DEVELOPMENT OF NEW METHODS AND TECHNIQUES FOR EARLY DIAGNOSIS AND THERAPEUTIC INTERVENTION, AND ALSO TO THE STUDY OF THE EPIDEMIOLOGY AND NATURAL HISTORY OF VARIOUS LUNG DISEASES.

II. Progress relative to the problems of respiratory disease is limited because of a dearth of manpower trained in the fundamental sciences as well as clinical medicine.

TRAINING PROGRAMS SHOULD BE DEVELOPED TO MEET NEEDS FOR MANPOWER CAPABLE OF ENGAGING IN FUNDAMENTAL MULTIDISCIPLINARY RESEARCH RELEVANT TO RESPIRATORY DISEASES.

OTHER TRAINING PROGRAMS SHOULD BE DEVELOPED TO MEET NEEDS FOR MANPOWER IN CLINICAL INVESIGATIONS THAT USE THE MOST SOPHISTICATED TECHNIQUES FOR PATIENT CARE.

PHYSICIANS AS WELL AS ALLIED HEALTH PERSONNEL SHOULD BE TRAINED IN LUNG DISEASE TO ASSURE DISSEMINATION AND APPLICATION OF AVAILABLE INFORMATION AT THE LEVEL OF COMMUNITY MEDICINE.

III. In most instances, the presently available supportive mechanisms are not suitable for the development of new scientific objectives emphasized by the Task Force.

CENTERS SHOULD BE DEVELOPED WHERE MULTIDISCIPLINARY RESEARCH AND TRAINING IN THE FUNDAMENTAL MECHANISMS THAT UNDERLIE PULMONARY DISEASES CAN LEAD TO NEW DEVELOPMENTS IN CLINICAL RESEARCH AND THEIR APPLICATION TO THE CARE OF PATIENTS.

MECHANISMS SHOULD BE DEVELOPED TO PROMOTE COOPERATION AND COLLABORATION BETWEEN INSTITUTIONS AS WELL AS BETWEEN PROGRAMS ENGAGED IN FUNDAMENTAL AND APPLIED MULTIDISCIPLINARY RESEARCH.

PANEL I

CHEMICAL STRUCTURE AND FUNCTION OF THE LUNG

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CHEMICAL STRUCTURE AND FUNCTION OF THE LUNG

INTRODUCTION

Over the past three decades much has been learned of the physiological behavior of the lung and its derangement in disease. The physiological capacities of the lung and thorax that relate to ventilation, distribution of air and blood (1), diffusion of gases (2), pulmonary hemodynamics (3) and mechanical characteristics of airways and alveoli (4) have been quantified and interrelated. Although this information has provided clinically useful insights into the patterns of physiological dysfunction of the lung, these long-standing directions of research have not elucidated the precise basis of disease. Such deranged patterns of respiratory function, while frequently life threatening, are usually the result, rather than the cause of pulmonary diseases. The missing links are alterations at the cellular, structural and molecular level which lead to altered pulmonary function. Virtually nothing is known of the manner in which pathogenetic processes produce destruction and alteration of the architecture of the lung, or of the functions of the diverse classes of lung cells which are essential to its normal function and to its role in the physiological balance of the whole organism.

Because of this lack of fundamental information, treatment of chronic pulmonary diseases along with their attendant alterations in pulmonary circulation are often ineffective once the disease is established. Moreover, we do not know how to prevent these diseases. It is necessary to have a deeper understanding of the chemical processes and chemical structure of the lung that maintain its physiological integrity and which are involved in the mechanisms of injury. Chemical processes should be investigated both as etiological mechanisms of disease and as altered functions once pulmonary morphology or physiology is deranged. This concept links the chemical processes of the lung to the physiological function of the lung in the whole organism.

CURRENT STATE OF KNOWLEDGE

Connective Tissue Structure of Lung Parenchyma and Airways

Although it has been known for many years that the lung is rich in collagen and elastin (5,6), chemical identification and quantification of these substances are at a preliminary stage of understanding and the analytical methods used have been imprecise. The distinctive physical characteristics of these components contribute to the distensibility, collapsibility and tensile strength of lung tissue (7), and they form a geometric framework for the morphology of alveoli, airways, blood vessels and their attendant cells.

In most forms of chronic airway obstructive disease some destruction of lung parenchyma occurs, and, in pure emphysema, lung tissue dissolution is a primary process of unknown etiology (8). Similarly in fibrotic reactions of the lung, connective tissue growth with distortion of lung architecture is a prominent feature. But fundamental questions are still to be answered. These include: 1) the quantities of connective tissue components in normal lungs, and differences in their quantitative distribution in various portions of the lung with age, sex, and environmental influences; 2) the amino acid composition of collagen and elastin in lung tissue, their chemical precursors, and their possible variations with age, sex and environmental influence, 3) variations in quantity and amino acid composition of connective tissue components of the lung in diffuse pulmonary fibrosis and in various types of airway obstructive disease, particularly pulmonary emphysema and chronic bronchitis; 4) the manner in which surface forces of the lining of alveoli and small airways interact with the mechanical characteristics of elastin and collagen within the interstitium, to produce observed physiological characteristics of stretch and collapse of the whole lung and within lung regions; 5) the sites of synthesis and rates of synthesis and degradation of elastin and collagen in the normal and diseased lung; 6) the in vivo balance and interactions between proteolytic enzymes with potential for structurally altering elastin and collagen at the molecular level, and the processes of synthesis, degradation, and destruction occurring normally and in lung disease. Answers to these questions are essential to an understanding of the pathogenesis of obstructive airway disease, but are equally important for elucidating the mechanisms of injury and repair in other forms of pulmonary disease, such as diffuse interstitial fibrotic reactions of the lung, bronchiectasis, asthma, respiratory distress syndrome of the newborn, and cystic fibrosis.

Pulmonary tissue substrates should be more fully investigated. While it is known that alveolar walls consist of at least four components (9) -- collagen, basement membrane collagen, elastic fibers and other protein components (consisting in part of glycoproteins) -- their proportions and specific amino acid structure are undefined. In vivo investigation of their rates of synthesis and turnover, utilizing radioactive proline and lysine, should be encouraged. And clinical studies, utilizing urinary connective tissue components to define altered turnover rates of connective tissue in pulmonary disease, should be explored, as they are potentially useful methods for screening and for understanding pathogenesis.

The normal quantities and types of protein components of alveolar walls as well as bronchi and bronchioles in various portions of the lung should be studied. The consistency, as well as inconsistencies, of protein composition and structure in the normal lung, and variations with age, sex, and environment may be important for understanding patterns of pulmonary destruction in obstructive lung disease. Recent work (10) has corroborated that elastin in the pleura increases with age as compared with the parenchyma, and has shown similar changes in amino acid composition of elastins in aorta and lung, but, the physiologic or pathogenetic consequences of such changes with age are unknown.

Because of the complex structure of lung tissue, it is particularly difficult to isolate and quantify pure connective tissue components. Present methods are both crude and drastic: Current isolation procedures, which involve use of sodium hydroxide at room temperature or at 100°C, could remove components which are critical to an evaluation of protein structure. Simpler techniques of isolation and identification would aid materially in efforts to define connective tissue components in populations, in various animal species, and in disease. Studies to identify structural changes in connective tissue fibers in situ in the lung should also utilize the potential available in light and electron microscopy to correlate fiber structure and chemical structure.

Experimental models should be investigated, using available biological techniques for altering connective tissue structure in predictable and measurable ways, to elucidate the relationship between chemical structure and function. Such techniques involve in vivo and in vitro exposure of whole lung, or selected portions, to proteolytic enzymes such as elastase, collagenase, papain, thermolysin, hyaluronidase and others. However, it should be noted that only limited information may be obtained from the use of these enzymes unless their anatomic and physiological effects are defined chemically. Other available models involve the alterations of connective tissue structure and synthesis induced by controlled dietary insufficiencies (e.g., lathyrism (11) and vitamin C deficiency) or by chemical substances which block chemical synthesis of collagen (e.g., penicillamine) (12).

Tissue culture preparations of alveolar cells may be used to induce formation of alveolar basement membrane components and their precursor compounds. These could then be compared chemically with isolated basement membranes from various animal lungs, lungs with obstructive airway disease, emphysema and fibrotic or proliferative reactions of lung parenchyma. Whole lung cultures may also be useful models to study detailed mechanisms of synthesis and degradation of collagen, elastin, and glyco-proteins, as these processes may not readily be investigated in vivo.

Disease states in man which are presumed to have a basis in tissue structural abnormalities can provide tissue specimens for analysis to determine chemical-pathological correlations. Such diseases include chronic bronchitis and emphysema, alpha$_1$ antitrypsin deficiency lung disease (13), Marfan's syndrome (12), inherited hydroxylysine deficient collagen (14), bullous disease of the lung, and diffuse interstitial pulmonary fibrosis.

Chemical-physiologic correlations in the normal and abnormal lung require close collaboration among biochemists, physiologists and bioengineers. The objective should be to interpret changes in the physiological functions of the lung in terms of molecular structure and integrated function of molecular components. Such studies should define the in vivo mechanics of the whole lung and its regions in terms of their precise chemical composition. Also, air flow, blood flow, and gas exchange

may be defined ultimately in terms of chemical structure and function of each organ component and their interrelationships. Such analyses might provide useful clinical insights into the structural predispositions to injury of specific lung regions and lung tissue components.

Chemical Mechanisms of Pulmonary Injury

Functional disturbances of the lung in various types of chronic lung disease may be due to irreversible structural alterations in various tissues of the lung, but we have no clear notion of the mechanisms which initiate and perpetuate them. There may be many types of lung tissue injury and these may depend upon structural differences in, for example, alveolar tissue as compared with the walls of bronchi or blood vessels.

Within the last decade a potential mechanism of lung injury has been identified, as more has been learned about pulmonary emphysema associated with inborn alpha$_1$ antitrypsin inhibitor deficiency in humans (13). Imbalances between proteolytic activity, and its control or inhibition may have profound implications as a generalized mechanism of lung injury (15) in other pulmonary pathological states, such as those related to infection (16), air pollution (17) or the respiratory distress syndrome of the newborn (18). Key questions with regard to this mechanism in the pathogenesis of obstructive lung disease include: 1) Are predispositions to lung disease due to overproduction of proteolytic enzymes, or qualitative differences in chemical potency, or release of these enzymes in individuals who are prone to chronic lung disease? Or, conceivably, do the initiating causes of lung injury involve environmental toxins which may induce changes in the production or the type of proteolytic agents in circulating polymorphonuclear leukocytes or alveolar macrophages? 2) What are the early and late structural effects on collagen, elastin and glycoproteins of these agents? Do different susceptibilities to reactions with proteolytic enzymes exist with regard to age, sex, ethnic background and environment? 3) What are the chemical characteristics of proteases having access to the lung under normal and certain pathological circumstances? 4) What are the characteristics of circulating leukocytes and the alveolar macrophage with respect to population, turnover, and migration to the lung from the bone marrow? 5) What are the mechanisms by which lysosomes release proteolytic enzymes? 6) What are the chemical interactions between the gaseous and solid products of smoking and the lysosomal function of macrophages?

Studies are needed to: 1) identify and characterize the chemical reactivity of proteolytic substances having access to the lung from serum, leukocytes, alveolar macrophages, platelets, and cathepsins of tissue origin; 2) further characterize the structure, chemical reactions, and turnover of the serum inhibitors of proteolysis; 3) explore the effects of deficiencies of α_1 globulin in animal models by means of virtual depletion of α_1 globulin inhibition by specific α_1 antiserum; 4) explore the chemical and physiological effects of proteolytic enzymes administered experimentally to overcome existin circulating or lung tissue inhibition. Such enzyme studies may include purifi

elastases, collagenases, other proteases and hyaluronidase, taking into account their limited specificity for substrates, and analyzing tissues chemically as well as ultrastructurally to assess the effects at the molecular level.

A more subtle form of pulmonary injury and of potential pulmonary dysfunction, are the cell turnover rates of functioning cells in the alveolus, endothelium and bronchus(19). Alterations in cell turnover or replacement may lead to biological dysfunctions of the lung. Alternatively, disease processes which start by independent mechanisms may ultimately express pulmonary dysfunction in terms of alterations in cell turnover. Relatively few studies have been performed in this field.

Genetic deficiency of alpha$_1$ antitrypsin should be studied in terms of biochemical changes. While it is recognized that the majority of individuals with chronic obstructive lung disease have a normal proteinase inhibitor genotype (pi_{mm}) (20), the incidence of obstructive lung disease and emphysema in individuals who have the genotype associated with severely deficient alpha$_1$ antitrypsin (Pi_{zz}) may be as high as 60% in those below age 60 (21). This genetic association is a useful tool to investigate the interplay of genetic and acquired or environmental factors in the production of obstructive lung disease and focuses on the possible role of proteolytic mechanisms and their inhibition as a basis for pulmonary injury.

The deficiency of alpha$_1$ antitrypsin in the serum of individuals with the Pi_{zz} genotype may stem from failure of the liver cells to release this protein after synthesis rather than an inability to synthesize the molecule (22). In this regard precise identification of the amino acid sequences of the α_1 globulin inhibitor in Pi_{zz} as compared with Pi_{mm} or Pi_{ss} and other variants should be of the highest priority to 1) understand the genetic abnormality at a more fundamental level and 2) to investigate mechanisms of release of alpha$_1$ antitrypsin from liver cells in the hope of preventing or interrupting the course of the disease.

Among the multiple causes of obstructive lung disease, the possibility exists that there are genetically determined structural features or cellular metabolic features of the lung which place a segment of the population at risk to develop airway obstruction or lung destruction when brought into contact with a particular set of environmental or pathologic factors.

Structure, Synthesis and Physical Characteristics of Bronchial Mucus

Increased production of bronchial mucus and an inability to clear the airways of secretions are critical pathological factors in many common diseases of the lungs such as chronic bronchitis, cystic fibrosis, asthma, acute respiratory distress syndrome and infectious pneumonitis. Effective treatment of these diseases requires an ability to control the viscosity, rate

of production and methods of elimination of mucus. There is very little information at present on these factors (23). Further work on the fundamental chemistry and pharmacology of mucus production is essential to an improved potential for dealing with these crucial aspects of the pathogenesis of lung diseases (24).

Bronchial secretions consist almost entirely of water which is so organized in the structure that it does not flow freely through the gel. The organization of water in the gel structure of bronchial secretions is one of the important factors affecting the consistency of secretions. Therefore, more information is required on how chemical agents may change sputum consistency by altering the hydrogen bonding of the water incorporated in the gel. Present information indicates that the gel structure of bronchial secretions includes a basic protein and two types of glycoprotein which are cross-linked to one another by disulfide bonds (25). The disulfide bonds can be disrupted by sulfhydryl agents such as N-acety-l cysteine or dithiothreitol which in turn also alters the consistency of secretions. However, there is no information as to where the disulfide cross-linkage takes place, whether before or after secretions, and by what chemical process.

Similarly little is known of the factors which control elasticity and viscosity of secretions, factors which are not mutually dependent and can be influenced separately (26). Of particular relevance is the effect of purulence on the physical properties of sputum and the effect of atmospheric pollutants such as tobacco smoke on the production and chemical composition of bronchial secretions. Information is also needed on the specific glycoproteins which provide a skeletal framework for the gels of bronchial secretions.

Finally, studies of bronchial mucus, chemical structure and physical characteristics will have to be related to the mucociliary clearance functions of the tracheobronchial tree to understand the basis of pathogenetic mechanisms involving bronchial clearance in disease (27).

Phospholipid and Protein Synthesis by the Lung

The potential of specific cells of the lung for phospholipid and protein synthesis and degradation is substantially unknown. Areas of ignorance with regard to phospholipid and protein synthesis which are especially relevant to the pathogenesis of common pulmonary diseases (28) are as follows: 1) The normal composition of surface active material is unknown, although it is generally agreed that dipalmitoyl lecithin is an essential component of surface material (29-32). Since dipalmitoyl lecithin occurs not only in surfactant but also in membranes, methods to detect and quantify surfactant, which depend upon analysis of the concentration of dipalmitoyl lecithin alone, may be misleading. Better methods for detection and quantification of surfactant should be sought. 2) Lack of knowledge of the normal structure of surfactant prevents thorough understanding of its

alterations in disease, and of the control or prevention of these alterations by physiological conditions in the lung. 3) Basic information is required on the pathways and mechanisms by which surfactant is dissipated or removed from alveoli.

Knowledge of the fundamental factors controlling turnover of surfactant could give insight into alveolar proteinosis, which appears to be a disease of excessive accumulation of surfactant, and into the respiratory distress syndrome, which is associated with reduced surfactant activity. In fact, it may not be possible to elucidate the mechanisms of these diseases until we have a more fundamental body of information on surfactant.

The need for studies on the synthesis of structural proteins such as collagen, elastin, and glycoproteins has already been mentioned. However, the potential of lung tissue for synthesis of proteins may be fundamental to a number of important chemical processes of the lung. The range and form of protein synthetic reactions, and the specific cells in which synthesis takes place, must be elucidated for complete understanding of the functions of the lung. Studies which may lead to characterization of new chemical reactions in lung tissue should be fostered (even though their relevance is not presently evident) since they may take on new significance as further knowledge is gained. This concept is further elaborated below.

Intermediate Metabolic Functions by Lung Tissue

The potential of parenchymal cells of the lung for a broad range of chemical processes is just beginning to be appreciated (33). These chemical mechanisms may be necessary for the normal physiological functions of the lung and may also play a role in the chemical and metabolic balance of other organs, other parts of the vasculature, and, possibly, in the capacity of the lung to deal with atmospheric pollutants. Mechanisms of importance with respect to understanding clinical pulmonary disease include: 1) identification of the chemical substrates normally utilized by the lung for tissue survival and normal pulmonary function; 2) the role of pulmonary blood flow in providing these substrates; 3) metabolic pathways utilized by the lung to protect it against atmospheric pollutants and the high oxygen tension to which alveolar tissue is exposed. The latter problem bears directly on the mechanisms of oxygen toxicity for the lung. Definition of these metabolic pathways also bears directly on the acute and chronic effects of exposure to tobacco smoke on the lung parenchyma.

Several aspects of this intermediary metabolism of the lung have just begun to be examined and may be fundamental to an understanding of the effects of pulmonary injury of diverse etiology. Examples include the biochemical and physiological basis and consequence of high lactate production by lung paraenchyma (34); the redox states of various systems in the lung; and the chemical, physiological and structural significance of the pentose pathway of the lung.

The mammalian lung actively participates in de novo synthesis of fatty acids (35,36), esterification of lipids (37) and the hydrolysis of lipid esters (38). Recently it has been demonstrated that lung slices can incorporate radioactivity from ethanol into lipids, the major fraction going to phospholipids (39). While it is recognized that lipid synthesis by the lung is directed largely to the formation of phospholipids, the full range of reactions concerning lipids as primary substrates or as end products remains to be explored.

It is now recognized that the lung has the capacity to elaborate or inactivate several compounds which have rapid, highly potent effects on bronchial and vascular smooth muscle (40). These substances include: prostaglandins, kinins, and angiotensin II derived from angiotensin I. Despite the large capacity of the lung to perform marked chemical alterations in these components in the course of one circulation through the lung, it is not clear what cells perform these functions and by what mechanisms. It is further not realized what the consequences for lung function and circulatory function are when lung parenchyma is destroyed or altered by disease, or when blood flow bypasses lung parenchyma as in congenital cardiac defects. Answers to these questions may define this functional capacity of the lung which can be quantified and characterized in pulmonary emphysema, chronic bronchitis, pulmonary fibrosis and alveolitis, asthma, as well as primary vascular diseases of the lung.

Glycoprotein Structure of the Lung

Glycoprotein structure of basement membrane varies greatly in different organs; for example, lung basement membrane resembles that of the choroid plexus of the central nervous system more than the basement membrane of the glomerulus or Descemet's membrane of the eye (41). The basement membrane of the lung has very special characteristics with respect to diffusion of respiratory gases or electrolytes and environmental gases. The biochemical structure of normal lung basement membrane with respect to its permeability characteristics has not been defined in man and we have no information on its changes with advancing age or disease.

Chemical characterization of lung basement membrane is a necessary first step to understanding the immune potential in certain diseases of the lung which make the basement membrane a target for pathogenic processes, such as Goodpasture's syndrome and the Hamman-Rich syndrome.

In this regard experimental models providing embryonic tissues may be used to define the components and their origin in the basement membrane. Similarly, tissue culture preparations of whole lungs or of cell lines of pulmonary origin would be experimentally useful. Such studies may be of fundamental importance in understanding the function, structural components and mechanisms of disease of the basement membrane of the lung in the mature organ.

Special Problems of Implementing Studies on Chemical Structure and Function of the Lung

The major proportion of investigative work on the physiology of the lung and its diseases has been by individuals whose training has been in respiratory physiology or clinical pulmonary medicine. To undertake fundamental, and yet clinically relevant, studies of the chemical structure and functions of the lung will require collaborative efforts between individuals in fundamental biochemistry, who have the techniques and insights into chemical mechanisms, and individuals in physiology, pathology, and medicine who can pose pertinent questions and provide interpretations of chemical data which may be translated into physiological and clinical insights. It is necessary to establish the means whereby individuals who are interested in diseases of the lung may be trained in its biochemical aspects. This will require training programs in which laboratories devoted to biochemical research may undertake the training of individuals in chemistry who have an orientation toward the functions of the lung from the physiological and clinical standpoint. Funding for training purposes should incorporate mechanisms which facilitate and encourage this collaboration between laboratories involved in biochemistry and laboratories and clinical centers concerned with pulmonary physiology and lung diseases. Recognition of the need for individuals to study the chemical structure and function of the lung implies the need to increase the manpower pool of persons with interdisciplinary training.

There is also a need for individuals at the level of senior investigators, who have shown a capacity for undertaking work in the chemical structure and function of the lung. Mechanisms are needed which will allow them to pursue their interests without the distractions of other work, and to supervise and stimulate work in this area by young individuals undergoing training.

For certain aspects of understanding of the chemical composition and function of the lung, chemical data will have to be interpreted in terms of dynamic structural characteristics. For such efforts, collaboration between individuals with orientations in engineering, structural physics, physiology and biochemistry are essential. Without a firm and longstanding commitment to collaborative efforts of this type, it is doubtful that a meaningful beginning or long-term effort can be made to relate the basic knowledge required with regard to chemical composition and structure of the lung to the diseases of the lung.

CONCLUSIONS

I

Lung parenchyma and airways are richly endowed with connective tissue, but little is known about the chemistry, physical properties, or sites and

rates of synthesis and degradation of its collagen and elastin components. Such information is essential to an understanding of the chemical and histological structure and function of the lung in health and disease.

Investigations should focus on lung histology, and the chemistry and metabolism of collagen and elastin in normal subjects, patients with various pulmonary diseases, and individuals with genetic predisposition to particular diseases. Particular attention should be directed to alterations with age, sex and environmental influences.

II

Alterations in proteins and cells associated with dissolution, fibrosis and distortion of lung tissue as a consequence of injury are poorly understood. Studies are needed on: (1) proteolytic enzymes and their naturally occurring inhibitors in circulating leucocytes, alveolar macrophages, platelets, serum and lung tissue; (2) synthesis and chemical and physical characteristics of bronchial mucus; (3) turnover rate of various types of lung cells; (4) the chemistry of surface active material of lung cells;and (5) metabolic pathways available in the normal and diseased lung.

Biochemical and histological investigations should be addressed to the roles of proteins, phospholipids, enzymes and cells implicated in mechanisms of lung injury.

III

Investigation of the chemistry and function of the lung depends upon many disciplines: medicine, physiology, chemistry, immunology, pathology. But there is a dearth of investigators with multidisciplinary training who can participate in this type of research.

Training programs are needed to develop investigators with interest in pulmonary problems and with knowledge of fundamental disciplines essential to the study of lung chemistry, structure and function.

RECOMMENDATIONS

Progress in treatment and prevention of lung diseases is limited by lack of information about alterations in the structure and function of the lung at the chemical and molecular level. Such fundamental derangements may be common to different pulmonary diseases, e.g.,chronic obstructive lung disease, asthma, infectious pneumonitis, hypersensitivity pneumonia, cystic fibrosis and respiratory distress syndrome. These basic problems are receiving inadequate attention. This is in part due to the lack of trained persons who can undertake multidisciplinary research and who are also interested in problems of diseases of the lung.

I

RESEARCH PROGRAMS SHOULD BE PROMOTED TO STUDY ALTERATIONS AT THE TISSUE, CELLULAR, AND MOLECULAR LEVEL THAT ARE ASSOCIATED WITH LUNG INJURY.

II

PROGRAMS SHOULD BE DEVELOPED TO ATTRACT AND TRAIN INVESTIGATORS IN DISCIPLINES NECESSARY FOR RESEARCH ON PULMONARY STRUCTURE AND FUNCTION. SUCH TRAINING SHOULD INCLUDE THE DISCIPLINES OF BIOCHEMISTRY, BIOPHYSICS, MORPHOLOGY AND PHYSIOLOGY AS WELL AS CLINICAL MEDICINE.

REFERENCES

1. Rahn, H. and Farhi, L.E.: Ventilation, Perfusion and Gas Exchange: The $\dot{V}_A/\dot{Q}$ Concept. In *Handbook of Physiology. Sec. 3. Resp. Vol. 1.* eds. W.O. Fenn and H. Rahn. Am. Physiol. Society. pp. 735-766, 1964

2. Forster, R.E.: Exchange of Gases between Alveolar Air and Pulmonary Capillary Blood: Pulmonary Diffusing Capacity. Physiol. Rev. 37: 391-452, 1957.

3. Fishman, A.P.: Respiratory Gases in the Regulation of the Pulmonary Circulation. Physiol. Rev. 41: 214-250, 1961.

4. Mead, J.: Mechanical Properties of Lungs, Physiol. Rev. 41: 281-330, 1961.

5. Briscoe, A.M. and Loring, W.E.: Elastin Content of Human Lung. Proc. Soc. Exp. Biol. Med. 99: 162-164, 1958.

6. Pierce, J.A. and Hocott, J.B.: Studies on the Collagen and Elastin Content of Human Lungs. J. Clin. Invest. 39: 8-14, 1960.

7. Turino, G.M., Lourenco, R.V. and McCracken, G.: Role of Connective Tissues in Large Pulmonary Airways. J. Appl. Physiol. 25: 645-653, 1968.

8. Ebert, R.V. and Pierce, J.A.: Pathogenesis of Pulmonary Emphysema. Arch. Intern. Med. 111: 34-43, 1963.

9. Fitzpatrick, M.: Studies of Human Pulmonary Connective Tissue. Am. Rev. Resp. Dis. 97: 248-256, 1968.

10. John, R. and Thomas, J.: Chemical Composition of Elastins Isolated From Aortas and Pulmonary Tissues of Humans of Different Ages. Biochem. J. 127: 261-269, 1972.

11. Piez, K.A.: Cross-Linking of Collagen and Elastin. Ann. Rev. Biochem. 37: 547-570, 1968.

12. Grant, M.E. and Prockop, D.J.: The Biosynthesis of Collagen (Part III). New Eng. J. Med. 286: 291-300, 1972.

13. Erickson, S.: Pulmonary Emphysema and Alpha$_1$ Antitrypsin Deficiency. Acta Med. Scand. 175: 197-205, 1964.

14. Pinnell, S.R., Krane, S.M., Kenzora, J.E., and Glimcher, M.J.: Heritable Disorder with Hydroxylysine Deficient Collagen. New Eng. J. Med. 286: 1013-1020, 1972.

15. Turino, G.M., Senior, R.M., Garg, B.D., Keller, S., Levi, M.M., and Mandl, I.: Serum Elastase Inhibitor Deficiency and Alpha$_1$ Antitrypsin Deficiency in Patients with Obstructive Emphysema. Science. 165: 709-711, 1969.

16. Falk, G.A. and Briscoe, W.A.: Alpha$_1$ Antitrypsin Deficiency in Chronic Obstructive Pulmonary Disease. Ann. Int. Med. 72: 427-429, 1970.

17. Freeman, G. and Haydon, G.B.: Emphysema after Low Level Exposure to NO_2. Arch. Environ. Health. 8: 125-128, 1964.

18. Evans, H.E., Levi, M., and Mandl, I.: Serum Enzyme Inhibitor Concentrations in the Respiratory Distress Syndrome. Amer. Rev. Resp. Dis. 101: 359-363, 1970.

19. Evans, M.J., Stephens, R.J., and Freeman, G.: Effects of NO_2 on Cell Renewal in the Rat Lung. Arch. Int. Med. 128: 57-60, 1971.

20. Fagerhol, M.K.: Quantitative Studies on the Inherited Variants of Alpha$_1$ Antitrypsin. Scand. J. Clin. Lab. Invest. 23: 97-103, 1969.

21. Kueppers, F., Fallat, R., and Larson, R.K.: Obstructive Lung Disease and Alpha$_1$ Antitrypsin Deficiency Gene Heterozygosity. Science. 165: 899-901, 1969.

22. Sharp, H.L.: Alpha$_1$ Antitrypsin Deficiency. Hosp. Prac. 6: 83-96, 1971.

23. Kwart, H. and Shashowa, V.E.: The Structure and Constitution of Mucus. Trans. N.Y. Acad. Sci. 19: 595-612, 1957.

24. Lieberman, J.: Enzymatic Dissolution of Pulmonary Secretions. Amer. J. Dis. Child. 104: 342-348, 1962.

25. Havez, R., Deminatti, M., Rousel, P., Randoux, A., and Biserte, G.: Etude des Glycoproteins Carboxyliques et Sulfates de la Secretion Bronchique Humaine. Clin. Chim. Acta. 17: 463-477, 1967.

26. Dulfano, M.J., Adler, K., and Phillippoff, W.: Sputum Viscoelasticity in Chronic Bronchitis. Amer. Rev. Resp. Dis. 104: 88-89, 1971.

27. Lourenco, R.V., Klimek, M.C., and Borowski, C.J.: Deposition and Clearance of 2 Micron Particles in the Tracheobronchial Tree of Normal Subjects - Smokers and Nonsmokers. J. Clin. Invest. 50: 1411-1420, 1971.

28. Massaro, D., Weiss, J., and White, G.: Protein Synthesis by Lung Following Pulmonary Artery Ligation. J. Appl.Physiol. 31: 8-14, 1971.

29. Pattle, R.E.: Surface Lining of Lung Alveoli. Physiol. Rev. 45: 48-79, 1965.

30. Clements, J.A.: Surface Phenomena in Relation to Pulmonary Function. Physiologist. 5: 11-28, 1962.

31. Scarpelli, E.M., Clutario, B.C., and Taylor, F.A.: Preliminary Identification of the Lung Surfactant System. J. Appl. Physiol. 23: 880-886, 1967.

32. Morgan, T.E.: Pulmonary Surfactant. New Eng. J. Med. 284: 1185-1193, 1971.

33. Hueter, F.G. and Fritzhand, M.: Oxidants and Lung Biochemistry. Arch. Int. Med. 128: 48-53, 1971.

34. Tierney, D.F.: Lactate Metabolism in Rat Lung Tissue. Arch. Int. Med. 127: 858-860, 1971.

35. Nasr, K. and Heinemann, H.O.: Lipid Synthesis by Rabbit Lung Tissue in Vitro. Amer. J. Physiol. 208: 118-121, 1965.

36. Salisbury-Murphy, S., Rubenstein, D., and Beck, J.C.: Lipid Metabolism in Lung Slices. Am. J. Physiol. 211: 988-992, 1966.

37. Popjack, G. and Beekmans, M.: Extra-Hepatic Lipid Synthesis. Biochem. J. 47: 233-238, 1950.

38. Heinemann, H.O.: Free Fatty Acid Production by Rabbit Lung Tissue in vitro. Am. J. Physiol. 201: 607-610, 1961.

39. Thomas, T. Jr., and Massaro, D.: Lipid Biosynthesis from Ethanol by Rabbit Lung. Amer. Rev. Resp. Dis. 106: 271-272, 1972.

40. Vane, J.R.: The Release and Fate of Vaso-Active Hormones in the Circulation. Brit. J. Pharm. 35: 209-242, 1969.

41. Kefalides, N.A. and Denduchis, B.: Structural Components of Epithelial and Endothelial Basement Membrane. Biochemistry. 8: 4613-4621, 1969.

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ENVIRONMENTAL DISEASES

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ENVIRONMENTAL DISEASES

INTRODUCTION

In the context of this report, environmental factors are broadly interpreted to include not only exogenous physical, chemical, and biological substances that pollute the ambient environment, but also social factors such as occupations, and psychologic factors such as smoking habits that are implicated in the development of lung diseases. While environmental diseases as defined by this panel overlap with diseases addressed by other members of the Task Force, the emphasis in this report is on the effects of exogenous, etiologic agents rather than on the disease process.

MAGNITUDE OF THE PROBLEM

With the growth and increasing complexity of industry, many working people are exposed to dust, fumes, and vapors which may cause lung disease. The number of people affected is very large, albeit incompletely recorded (1). Populations at risk include: 250,000 workers regularly employed at the present time in segments of the asbestos industry; almost 200,000 coal miners; and 500,000 cotton textile workers in the country, of whom a significant proportion work in such areas as preparation, carding, spinning, and weaving, where as many as 25% of the workforce may suffer from symptoms or signs of byssinosis. The number of workers at risk as a result of exposure to cadmium oxide, beryllium, bagasse, toluene diisocyanate is not well established, and similar uncertainty exists concerning the extent of exposure to moldy hay or industrial enzymes. A recent estimate suggests that more than 500,000 workers are exposed to irritant gases and 1,100,000 to silica (2).

The increasing technological complexity of industry has introduced and will continue to introduce into the industrial environment a variety of exogenous agents implicated in the etiology of occupational lung disease. Moreover, the time-lag in identifying toxic agents is such that there is strong suspicion that many agents have not yet been identified. The hazard of exposure to cotton textile dust was established in this country only in the past decade; bentonite (long assumed to be an "inert" dust) has now been shown to produce severe lung disease among those mining it in Wyoming (3); and the biological potential of a widely used industrial chemical, bis(chloromethyl) ether, and of fine fibrous glass were only recently reported (4,5). The incidence of disabling pulmonary fibrosis among asbestos workers was not documented in this country until the 1960's.

Pulmonary asbestosis has been recorded in some surveys in 90% of older workers. Byssinosis has been demonstrated in the last five years in approximately one of four cotton textile workers in those groups that were studied. These examples may be multiplied many times by those exposed to silica, ozone, metal fumes, industrial enzymes, beryllium, chemical vapors, and talc.

The high incidence and serious nature of respiratory disease among cigarette smokers has been amply documented. As stated in the Surgeon General's first report (6) and again emphasized in the second (7): "Cigarette smoking is the most important of the causes of chronic bronchitis in the United States and increases the risk of dying from chronic bronchitis." The second report goes a step farther: "For the bulk of the population of the United States, the importance of cigarette smoking as a cause of chronic bronchial pulmonary disease is much greater than that of atmospheric pollution or occupational exposure." Some measure of the magnitude of the problem of respiratory diseases from smoking may be inferred from data from the National Center for Health Statistics: 69.3% of adult males and 42.8% of adult females had a history of regular cigarette smoking in 1970 (8). The Center has also recorded that emphysema afflicts approximately 1% of our total adult population, while bronchitis is found three times as frequently. Though well known, this information has had little influence on smoking habits of the population.

Data that characterize and define the nature and extent of chronic lung disease associated with community air pollution are meager and uncertain. Even when data on community air pollution are available their interpretation is unclear because of concomitant effects of smoking. Comparable samples of cigarette smokers in cities as widely different as New York, Bergen (Norway), Los Angeles, and London, have shown no major differences in the prevalence of cough and sputum. In the American Cancer Society's prospective study of over 1,000,000 people, residence showed only a minor influence, when cigarette smoking was taken into account (9). Pulmonary emphysema was relatively rare in a population of non-smokers who lived in an area of California with marked atmospheric pollution (10).

On the other hand, information from Great Britain indicates that among cigarette smokers atmospheric pollution exerts a measurable effect (11,12) reminiscent of the smoking effect on individuals with exposure to pneumoconiotic dusts (13-15).

CURRENT STATE OF KNOWLEDGE

Current mechanisms for obtaining epidemiological data are inadequate: The studies have been concerned mainly with prevalence and incidence rates, have long time lags, usually identify only gross disease, and have not employed available field methods for early detection in the population studied.

A paucity of firm data relevant to dose-disease response for any single etiologic agent or any combination of agents whether they be occupational, environmental or endogenous. These problems, although serious, are amenable to solution. Perhaps in no other group of diseases can translation of knowledge obtained by research into preventive and therapeutic measures be so confidently expected.

Etiologic Factors

The timelag in assessing the health impact of an etiologic factor after it has been identified has seriously hampered effective prevention of environmental disease. For example, although silicosis has been a well-defined disease for almost a century, only recently (2) has it been possible to estimate the number of workers exposed to silica. Efforts to control "black lung" were belated and delayed, a failure in no small part due to inadequate data on the magnitude of the problem. Even in 1971, no reliable data on mortality patterns among bituminous and anthracite coal miners in the United States were available (16). The high incidence of lung cancer and other neoplasms as well as disabling pulmonary fibrosis among asbestos workers was not documented in this country until the 1960's.

To prevent such lags in the future, it is important to initiate pilot epidemiologic studies of working populations exposed to substances of known toxicity but for which few or no epidemiologic data are available. Industry-wide surveys would be in order for the chemical industry, petroleum refineries, shipyards, and commercial agriculture. It might be well to add the printing trades, in view of the scattered reports of altered mortality patterns among workers in this industry (17). Initiation of such epidemiological research will likely include an important fringe benefit: the establishment of surveillance mechanisms for evaluation of pulmonary hazards of new materials. Rapidly developing technology carries with it the possibility that new agents capable of causing occupational lung disease will be widely introduced over rather short time-spans. It is important to detect such substances early. Appropriate physiological studies can be useful, especially if populations newly exposed can be defined and followed. Laboratory studies of suspect agents can include a variety of test systems. The least that can be expected from such an approach is documentation of a presumed innocuous nature. We should not risk omission of early detection of an important pulmonary disease hazard, and must not resort to the human test system of industrial workers as "nature's clinical experiment." The long time lag sometimes inherent in such an approach is no longer acceptable.

A recent example of the effectiveness of such approaches is a new occupational lung disease identified several years ago to be the result of exposure of workers to *B.subtilis* enzymes in detergent preparations. Rapid interaction among clinical studies of lung disease (18), epidemiological study (19), immunology (20), and a basic laboratory technique, radioimmunoassay (21), defined the problem and provided industry with sufficient knowledge to bring the situation under control.

Little is known of the submicroscopic particulate burden of community air, despite its potential importance. This area offers an exceedingly important new frontier for research (22), with relevance not only to industrial lung disease, but to atmospheric pollution as well. It may turn out that particles visible by light microscopy play a relatively minor role in human disease. Submicron particles

almost invariably accompany them, and may have much greater pathogenic significance. This is largely unstudied. In many instances the larger particles are absent, yet disease occurs with the presence of particles in the Angstrom range (23). In smoking, such fine particles may exert their effect either directly, by virtue of their specific chemical or physio-chemical nature, by acting as carriers for gaseous and other elements, or by interacting with other elements in cigarette smoke. An example of the potential importance of this largely unexplored field is that cigarette filters designed for gaseous components may be ineffectual for microparticles.

Research on fine particles provides a fertile field for collaboration and mutual fertilization between epidemiological and clinical studies, and laboratory investigation. The spectrum of potential interactions is wide. Research here can proceed in several ways, ranging from analytical studies of lung dust burden in various occupational circumstances, to physical measurements of suspect environments (24). Information gathered in any one of these will stimulate and guide research in others.

Multiple-Factor Etiology

Evidence has already established that interactions of two or more factors greatly increase the risk of occupational lung cancer (25,26) and pneumoconiosis (13-15). These fragmentary observations, however, are perhaps more important in suggesting a general rule. It may turn out to be that much occupational lung disease, and environmental lung disease in general, is not to be identified or well-studied by investigating single factors. It may also be that many industrial lung diseases would not occur except with the additive or even multiplicative effect of two or more agents. In such circumstances, it could be practical to focus on the elimination of the agent least difficult to control. Such knowledge would be immensely useful to industry.

In the past several years, a number of studies have demonstrated such interrelationships between cigarette smoking and other environmental factors. It has been demonstrated that miners exposed to crystalline silica tend not to suffer from chronic bronchitis unless they also smoke cigarettes; but when they smoke,the incidence of such disease is greater than among smokers in general (13). A similar interaction has been observed among workers exposed to cotton dust (14) or to asbestos fibers (15), where pulmonary fibrosis is more frequent and more extensive when cigarette smoking is added to the dust exposure. The importance of such observations is further emphasized by the knowledge that multiple-factor potential also exists for pulmonary carcinogens, as asbestos and uranium mining (25,26).

In addition to cigarette smoking,there are exposures to physical factors (such as high or low temperatures, dry or wet atmospheres, radiation of several types, and to physiological states (such as pregnancy, advanced age, poor nutrition). Infection may be important (27), as may be altered metabolic or genetic patterns (28). The fact that 5% of workers

regularly exposed to asbestos for more than 40 years still have normal chest x-rays (29) is good evidence for the existence of individual variation based upon factors other than exposure to this toxic agent.

Dose-Response Relationships

In all research concerning environmental lung diseases there should be greater emphasis on quantitative approaches that will establish dose-response relationships and determine "no-effect" levels of exposure. Many substances of great value to society are "toxic" at some level, in some circumstances. At other levels and in other circumstances such toxicity is either very infrequent or absent. For rational decisions to be made concerning utilization of such materials, and for evaluation of requirements for control, research is necessary to provide fundamental data concerning incidence of disease at various exposure levels.

In most instances, such dose-response relationships must be derived from research in occupational circumstances, especially when investigating diseases with a long lapse between exposure and onset of the disease. Nevertheless, the results will be applicable to respiratory disease which might be associated with atmospheric pollution in the general community. While there can be no automatic carryover of occupational "threshold levels" to circumstances of community exposure, the data will have relevance to general populations.

Fundamental Research

While epidemiologic investigations may define problems, provide clues about etiologic factors, and lead to immediate preventive measures and surveillance that will have long-range impact on therapy and prevention of environmental disease, such approaches should include studies of the nature of the fibrogenic reaction in lungs, pathophysiology of bronchial cells, physiology of pulmonary smooth muscle, and neural control of airways.

Allergic respiratory disease is a critical area for basic investigation. Immunologic studies of the house dust allergy mite would be of great value both clinically and to the field of allergy. Investigation of unusual allergens which may affect immune status (30) is a virtually unexplored field of considerable clinical and theoretical importance. In one form of occupational asthma a specific immunoglobulin has already been identified (31), and advances in this area may assist us in identifying hyperreactors to a number of industrially important substances, as toluene diisocyanate, cotton dust, moulds (farmer's lung, bagassosis), causes of a variety of forms of extrinsic allergic alveolitis, and industrial enzymes.

Immunological research addressed to the interaction of inhaled materials, connective tissue, pulmonary cells, and the lymphatic and vascular systems in the lung also holds promise. The rapid advances being made in

biological studies associated with organ transplantation may provide valuable leads for such investigations.

The discovery that in some individuals, deficiency of serum alpha$_1$ antitrypsin is associated with the development of disabling or fatal emphysema (28), opened a fertile field for investigation of the metabolic status of individuals and their reactions to respiratory irritants. Such research could extend far beyond enzymes and should include chemical mediator substances (32). Clarification of the role of such substances in byssinosis and asthma will have wide application in many types of environmental lung disease.

Information is badly needed concerning the mechanism of cigarette smoking damage. Here, it would be well to take advantage of the many advances in cellular biology that have been made in the past ten years. Some such studies are already in progress, including investigations concerning clearing mechanisms, ciliary action, and quantitative studies of bronchial cellular change. What have not been looked at carefully have been the determinants of individual response, including metabolism of cigarette smoke products, enzyme effects, variations in tissue repair. Are there inborn metabolic differences which result in one cigarette smoker developing serious pulmonary disease and another showing very little? It has been suggested that appropriate genetic and metabolic studies of siblings of cigarette smokers might provide useful information in this regard (33).

Population Studies

Epidemiologic investigations have tended to be cross-sectional and point-prevalence studies, with little recorded concerning the natural history of respiratory disease at various levels of air pollutants. These methodologic defects would not be difficult to remedy.

As noted above, more information is needed about the dose-response relationship. It cannot be assumed that there is necessarily a straight line relationship, which can be projected backwards from episodic disasters such as have occurred in London, Donora, or in the Meuse Valley. Indeed, the evidence so far available would suggest that defense mechanisms may be adequate in the presence of sufficiently low levels of air pollutants.

An important area for research is investigation of younger age groups, particularly children. Far too many studies on chronic lung disease have dealt only with older age groups, where the disease is usually irreversible and medical treatment of relatively little benefit. Extension of studies among children, moreover, will provide information of value in several ways. First there are scattered data which suggests that the initiation of environmental lung disease as a result of air pollution in childhood may be the starting point for continuation and progression of such disease in later life. The study of the natural

history of pulmonary disease associated with community air pollution should properly begin in childhood, and also to take into account such additional factors as residence, housing, nutrition, respiratory infections (34). Should a relationship be established between exposure to polluted air in childhood and subsequent increased risk of chronic lung disease, it will have identified an important point for the application of preventive measures (35).

Therapy

There has been little research on ameliorating or reversing the effects of occupational lung disease, or preventing its progression after removal from additional exposure. New leads have appeared and should be vigorously exploited: it has been demonstrated that at least one substance (polyvinyl pyridine N-oxide) can prevent silica fibrogenesis in the experimental animal even when administered after dust exposure (36). It is possible that the polymer exerts an intracellular protective effect. There is reason to believe that a variety of substances can affect the biological properties of pathogenic dusts, at least when tested in vitro. The promise of these observations should be vigorously explored and additional research stimulated on approaches to neutralize lung dusts in vivo.

CONCLUSIONS

I

In the spectrum of environmental diseases, cigarette smoking is the most important single cause of environmental lung disease, and is likely to be a major problem for at least two decades. The problem of cigarette smoking requires an immediate attack of greater scope than at present.

Epidemiologic studies should provide information on the natural history and progression of symptoms related to chronic bronchitis and emphysema, diseases that are attributed in large measure to cigarette smoking.

Research should be addressed to fundamental studies of the mechanism of damage from cigarette smoking, including studies on clearing mechanisms, ciliary actions, quantitative studies of bronchial cellular change, metabolism of cigarette smoke products, enzyme effects, and variations in tissue repair.

Studies on development of a safe cigarette should be encouraged, but greater attention should be directed to behavioral studies to learn how smoking habits can be altered.

II

With the growth and increasing complexity of industry in this country, large numbers of working people are exposed to environmental agents that may cause lung diseases. Rapidly developing technology carries the additional threat that new agents capable of causing occupational lung disease will be widely introduced over relatively short timespans. A national, broad research program is needed to investigate these occupational pollutants and to determine whether or not they are also threats to the general population.

Epidemiologic studies of occupational diseases should be quantified to establish dose-response relationships between etiologic agents and occupational diseases.

Studies of etiologic factors in environmental lung diseases should be designed to determine the possible additive effects of two or more agents, and particularly the interaction of cigarette smoking with other environmental factors.

Fundamental studies of occupational diseases should include studies of fine particles, which may also be a factor in the effects of cigarette smoking.

III

Respiratory diseases associated with air pollution in communities is a problem of undetermined magnitude and importance. Data from occupational diseases are not necessarily applicable to living conditions of the general population.

Studies of the natural history of pulmonary disease associated with community air pollution should begin in childhood.

Studies of communities should include assessments of dose-response relationship between polluted air and lung diseases.

IV

Investigations are needed on lung responses to environmental agents.

Fundamental research should include studies of the role of infection, enzymes, chemical mediators, immunologic reactions, and pulmonary pathophysiology.

RECOMMENDATIONS

AVAILABLE SUPPORTIVE MECHANISMS, INCLUDING SPECIALIZED CENTERS OF RESEARCH, SHOULD BE DRAWN UPON TO FOSTER MULTIDISCIPLINARY RESEARCH PROGRAMS ADDRESSED TO CIGARETTE SMOKING, OCCUPATIONAL LUNG DISEASES, AND ATMOSPHERIC POLLUTION.

THESE PROGRAMS MUST COMBINE EPIDEMIOLIGIC STUDIES WITH RESEARCH ON THE BASIC MECHANISMS OF PULMONARY RESPONSE TO ENVIRONMENTAL AGENTS.

REFERENCES

1. Trasko, V.M. and Worden, E.T.: Occupational Health Statistics in the United States. J. Indian Med. Prof. 7: 3454-3459, 1961.

2. Stelzer, D.F.: Personal Communication

3. Phibbs, B.P., Sundin, R.E. and Mitchell, R.S.: Silicosis in Wyoming Bentonite Workers. Amer. Rev. Resp. Dis. 103: 1-17, 1971.

4. Laskin, S., Kuschner, M., Drew, R.T., Cappiello, V.P. and Nelson, N.: Tumors of the Respiratory Tract Induced by Inhalation of Bis (chloromethyl) Ether. Arch. Environ. Health. 23: 135-316, 1971.

5. Stanton, M. and Wrench, C.: Mechanisms of Mesothelioma Induction with Asbestos and Fibrous Glass. J. Nat. Cancer Inst. 48: 791-821, 1972.

6. Smoking and Health. Report of the Advisory Committee to the Surgeon General. U.S. Department of Health, Education and Welfare, Public Health Service Publication No. 1103, U.S. Government Printing Office, Washington, D.C. 1969.

7. The Health Consequences of Smoking. A Report of the Surgeon General, U.S. Department of Health, Education and Welfare. U.S. Government Printing Office, 1971.

8. Health Interview Survey, National Center for Health Statistics. 1970.

9. Hammond, E.C. and Selikoff, I.J.: The Effects of Air Pollution: Epidemiological Evidence. Pneumoconiosis. Proceedings Int. Conf. Johannesburg 1969. ed., H.A. Shapiro, Oxford Univ. Press, Capetown. pp. 368-373, 1970.

10. Dysinger, P.W. and Lemon, F.R.: Pulmonary Emphysema in a Nonsmoking Population. Dis. Chest. 43: 17-25, 1963.

11. Holland, W.W. and Reid, D.D.: Urban Factor in Chronic Bronchitis. Lancet. 1: 445-448, 1965.

12. Lambert, P.M. and Reid, D.D.: Smoking, Air Pollution, and Bronchitis in Britain. Lancet. 1: 853-857, 1970.

13. Sluis-Cremer, G.K., Walters, L.G., and Sichel, H.S.: Chronic Bronchitis in Miners and Non-Miners; An Epidemiological Survey of a Community in the Gold-Mining Area in the Transvaal. Brit. J. Indust. Med. 24: 1-12, 1967.

14. Merchant, J.A., Kilburn, K.H., O'Fallon, W.M., Hamilton, J.D. and Lumsden, J.C.: Byssinosis and Chronic Bronchitis Among Cotton Textile Workers. Ann. Intern. Med. 76: 423-433, 1972.

15. Weiss, W.: Cigarette Smoking, Asbestosis and Pulmonary Fibrosis. Amer. Rev. Resp. Dis. 104: 223-227, 1971.

16. Enterline, P.E.: A Review of Mortality Data for American Coal Miners. Ann. N.Y. Acad. Sci. 200, in press, 1972.

17. Moss, E., Scott, T.S. and Atherley, G.R.G.: Mortality of Newspaper Workers From Lung Cancer and Bronchitis 1952-66. Brit. J. Industr. Med. 29: 1-14, 1972.

18. Flindt, M.L.H.: Pulmonary Disease due to Inhalation of Derivatives of Bacillus subtilis Containing Proteolytic Enzyme. Lancet. 1: 1177-1181, 1969.

19. Newhouse, M.L., Tagg, B., Pocock, S.J. and McEvan, A.C.: An Epidemiological Study of Workers Producing Enzyme Washing Powders. Lancet. 1: 689-693, 1970.

20. Pepys, J., Hargreave, F.E., Longbottom, J.L. and Faux, J.: Allergic Reactions of the Lungs to Enzymes of Bacillus subtilis. Lancet. 1: 1181-1184, 1969.

21. Berson, S.A., Yalow, R.S., Saito, T. and Selikoff, I.J.: Antibodies to "Alcalase" After Industrial Exposure. New Eng. J. Med. 284: 688-690, 1971.

22. Turkevich, J.: The World of Fine Particles. Amer. Sci. 47: 97-119, 1959.

23. Miller, A., Teirstein, A.S., Bader, M.E., Bader, R.A. and Selikoff, I.J.: Talc Pneumoconiosis: Significance of Sublight Microscope Mineral Particles. Amer. J. Med. 50: 395-402, 1971.

24. Selikoff, I.J., Nicholson, W.J. and Langer, A.M.: Asbestos Air Pollution. Arch. Environ. Health. 25: 1-13, 1972.

25. Selikoff, I.J., Hammond, E.C. and Churg, J.: Asbestos Exposure, Smoking and Neoplasia. JAMA. 204: 106-112, 1968.

26. Lundin, F.E., Jr., Lloyd, J.W., Smith, E.M. Archer, V.E. and Holaday, D.A.: Mortality of Uranium Miners in Relation to Radiation Exposure, Hard-Rock Mining and Cigarette Smoking, 1950 through September 1967. Health Physics. 16: 571-578, 1969.

27. Coffin, D.L. and Blommer, E.J.: Acute Toxicity of Irradiated Auto Exhaust. Its Indication of Enhancement of Mortality From Streptococcal Pneumonia. Arch. Environ. Health. 15: 36-38, 1967.

28. Eriksson, S.: Studies in $Alpha_1$ Antitrypsin Deficiency. Acta Med. Scand. Suppl. 177: 1-85, 1965.

29. Selikoff, I.J., Churg, J. and Hammond, E.C.: The Occurrence of Asbestosis Among Insulation Workers in the United States. Ann. N.Y. Acad. Sci. 132: 139-155, 1965.

30. Zarkower, A.: Alterations in Antibody Response Induced by Chronic Inhalation of SO_2 and Carbon. Arch. Environ. Health. 25: 45-50, 1972.

31. Coombs, R.R.A., Hunter, A., Jonas, W.E., Bennich, H., Johansson, S.G.O., and Panzani, R.: Detection of IgE (IgND) Specific Antibody (Probably Reagin) to Castro-Bean Allergen by the Red-Cell-Linked Antigen-Antiglobulin Reaction. Lancet. 1: 1115-1118, 1968.

32. Collier, H.O.J. and James, G.W.L.: Humoral Factors in Airway Function With Particular Reference to Anaphylaxis in the Guinea Pig. In: *Airway Dynamics: Physiological and Pharmacology*. ed., A. Bouhuys. Charles C. Thomas, Springfield, Ill. pp. 239-252. 1970.

33. Camner, P. and Philipson, K.: Tracheobronchial Clearance in Smoking Discordant Twins. Arch. Environ. Health. 23: 60-63, 1972.

34. Douglas, J.W.B. and Waller, R.E.: Air Pollution and Respiratory Infection in Children. Brit. J. Prev. Soc. Med. 20: 1-8, 1966.

35. Pearlman, M.E., Finklea, J.F., Creason, J.P., Shy, M., Young, M. and Horton, R.J.M.: Nitrogen Dioxide and Lower Respiratory Illness. Pediatrics. 47: 391-398, 1971.

36. Schlipkoter, H.W.: Possibilities of Causal Prophylaxis and Therapy of Pneumoconiosis. Arch. Environ. Health. 21: 181-191, 1970.

PANEL III

NON-ALLERGIC AIRWAYS DISEASES

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NON-ALLERGIC AIRWAYS DISEASES

INTRODUCTION

The panel addressed itself to promising areas of research in non-allergic diseases of the airways, research that might ultimately result in prevention, control and even cure of these disorders.

The scope of non-allergic diseases of the airways is difficult to define adequately. It includes: chronic bronchitis, defined as increased cough and sputum production without other cause; emphysema, defined as enlarged alveolar spaces with breakdown of alveolar walls; and bronchiectasis. However, non-allergic diseases in children and infants -- cystic fibrosis and bronchiolitis -- were not considered by the panel. The categories of chronic bronchitis and emphysema include conditions generally grouped under one or the other of the following rubrics: irreversible airways obstruction, chronic obstructive pulmonary disease, or small airways disease. These terms refer to conditions that are not generally reversible with therapy; their relationship to chronic bronchitis and emphysema, as defined above, is unclear. Increased cough and sputum production and enlarged airspaces with breakdown of alveolar walls may or may not by themselves lead to obstruction, yet they are usually associated with it.

MAGNITUDE OF THE PROBLEM

Death rates in the United States from respiratory disease have increased since 1958 only for malignancies, bronchitis (unqualified) and chronic bronchitis, and emphysema. In other categories, the death rate has declined or remained constant. For malignancy, the death rate between 1958 and 1967 increased by 41%; for unqualified and chronic bronchitis by 80%; and for emphysema by 172% (1). The leading causes of death from respiratory disease are malignancy and pneumonia, with death rates in 1967 of 29.3 and 28.0 per 100,000 respectively. For emphysema, the third leading cause of death, the rate in 1967 was 10.6 per 100,000.

Although data on deaths from pneumonia are not subdivided into predisposing underlying causes, it is a widely held clinical tenet that death from this disease is comparatively rare unless there is underlying disease, generally either heart failure or chronic obstructive lung disease . It is reasonable to assume that many deaths due to pneumonia would not have occurred if the patient had not suffered from underlying emphysema. Reliable statistics are not available on mortality and morbidity due to pneumonia in patients with chronic bronchitis and emphysema.

The socio-ecomomic impact of these diseases is extremely difficult to assess. The best available data are from 1967. The accuracy of mortality and morbidity statistics depends upon the accuracy of diagnosis which has been steadily improving over the years and may account for some of the increased incidence. Based on such limited statistical data, estimates of socio-economic costs are subject to very large errors.

For 1967, the estimated cost of morbidity and mortality due to bronchiectasis, chronic and unqualified bronchitis, and emphysema was $1.8 billion. Of this amount, the morbidity costs were $1.2 billion, including $655 million that represented loss of earnings. The estimated cost of all respiratory diseases, excluding cancer, was $6.3 billion for 1967. It is believed that about one-third of this total was due to underlying bronchitis and emphysema. In terms of man-years lost due to lung disease in 1967, it is estimated that chronic bronchitis and emphysema account for half of the total of 181,000 man-years. Thus, these diseases represent, in terms of both incidence and cost, the most important public health respiratory problems in the United States, and they are increasing at the most rapid and alarming rate as major causes of death.

CURRENT STATE OF KNOWLEDGE

Natural History

By the time they present with breathlessness or other symptoms, patients with chronic bronchitis or emphysema are at a comparatively advanced stage of their disease. There is no evidence that any therapeutic measures (including cessation of smoking) delay deterioration of ventilatory impairment and development of respiratory failure and cor pulmonale (2). On the basis of present knowledge, the physician can only provide symptomatic relief. In the absence of an unforeseen breakthrough there seems to be little gained by investigation of advanced disease using traditional methods. Study of end-stage disease leads to confusion as to what is cause and what is effect.

Much less is known about the earlier stages of these diseases although basic physiological studies in the last decade have now opened the way to such studies. The problem has been to establish the presence of impaired function in the peripheral airways within which obstruction develops from a variety of naturally occurring human diseases. Normally, peripheral airways contribute little to total pulmonary resistance so that considerable obstruction can be present within them with little impairment of lung function (3,4). As described below, however, newly applied tests of lung function have been found to be sensitive indicators of peripheral airway abnormality at a stage when routine tests of lung function are normal (3,5). Within the past two years, the use of these tests has shown that a substantial proportion of cigarette smokers are abnormal when compared to a control group of non-smokers (6). The lungs of smokers with peripheral airway obstruction behave asynchronously (3), have regional abnormalities, and evidence of airway closure at higher than normal lung volume (6).

In assessing abnormalities in "early" peripheral airway obstruction, a major problem is to define "normal" and "abnormal". Most normal values for routine tests of lung function include measurements in asymptomatic smokers as well as non-smokers. Yet asymptomatic smokers may have evidence of peripheral airway obstruction (7). When more normal values of routine tests become defined in a non-smoking population, the sensitivity of some of these tests may become improved. Many use frequency-dependence of compliance as a good criterion of abnormality, but there is not uniform agreement on this. A major problem with this test is that it requires meticulous matching of the frequency response characteristics of the flow and pressure measuring device, considerable cooperation by patients and tight control of other variables, such as lung volume and lung volume history. For these reasons it is virtually impossible to standardize and it is not surprising that different laboratories have found different results.

The technology is probably adequate for defining the natural history of chronic obstructive lung disease in its earlier stages. Such studies are urgently needed to answer the following important questions:

The first of these is reversibility. Cessation of smoking reverses frequency-dependence of compliance (7) and hypoxemia (8), although preliminary evidence suggests that the lung volume at which airways are thought to close is as high in ex-smokers as it is in smokers, and considerably higher than in non-smokers. This suggests that some of the earlier manifestations of these diseases are reversible and others are not.

The second question concerns the long-term significance of abnormalities found in these sensitive tests of lung function. It is unknown whether or not the future population of patients with advanced irreversible airways obstruction will come from population of smokers with evidence of abnormalities in peripheral airways. The answer to this question will require long-term prospective studies.

The third question is whether or not sensitive function tests can be used to define a group at high risk to develop chronic irreversible airways obstruction. This will also require short-term and long-term prospective.

Etiology and Pathogenesis

Numerous factors, both exogenous and endogenous, are implicated in the etiology of non-allergic airway disease. It is quite clear that cigarette smoking is the most important exogenous factor in

development of both chronic bronchitis and emphysema. Although air pollution also plays a role, it is secondary. While it is clear that almost all patients with end-stage obstructive lung disease are smokers, the fact that not all smokers develop severe pulmonary dysfunction indicates the importance of other factors in etiology. There is a sex difference in susceptibility to development of chronic irreversible airways obstruction but why females are less susceptible is unknown and largely unexplored. In this regard, the finding that progesterone protects against the development of papain-induced emphysema in experimental animals is of considerable interest (9). The role of previous disease of airways (such as bronchiolitis in childhood and repeated upper respiratory tract infections) and of aerodynamic factors (such as shear stresses during cough) in the etiology and pathogenesis of chronic airway disease requires definition (10).

Inherited genetic defects can predispose to both the development of peripheral airways obstruction (cystic fibrosis) and to emphysema (alpha $_1$ antitrypsin deficiency). Little is known of other genetic abnormalities which predispose to airways obstruction and emphysema, although familial chronic obstructive lung disease without cystic fibrosis or alpha $_1$ antitrypsin deficiency has been described. A virtually unexplored area of research is whether genetically and/or environmentally determined "normal" differences in structure and function, such as the normal variability in the ventilatory response to CO_2 and maximum expiratory flow rates, predispose to the development of disease. Although several hypotheses have been proposed as to why some subjects with airway disease develop respiratory failure, while others do not, this fundamental question remains unanswered (11).

Pathology

The pathological abnormalities of established emphysema are well-described although the earliest lesions are poorly understood (12). Those of chronic bronchitis are less well-described, although mucous gland hyperplasia and goblet cell metaplasia appear to be the characteristic abnormalities (13). Estimates of mucous gland hyperplasia are quantitative and, probably because of this, the pathological study of chronic bronchitis has focused on this lesion. However, physiological studies indicate that the site of obstruction to airflow is in the peripheral airways (4), where the major morphological abnormality is goblet cell metaplasia. There is need for quantitative morphology in this region of the lungs both in normal peripheral airways and in lungs with peripheral airway obstruction.

The general pathology of the lung, and how it can react to injury is not well documented, although knowledge of this crucial area is critical to the understanding of all lung diseases. With regard to emphysema, knowledge is needed as to whether alveolar wall breakdown is a non-

specific response to a variety of insults and derangements. Its production by proteolytic enzymes in experimental animals is well documented (14) as is its occurrence in individuals with alpha $_1$ antitrypsin deficiency (15). Emphysema has also been stated to result from a variety of other toxic agents although the resulting pathological abnormalities are less well documented. That goblet cell metaplasia is a nonspecific response to chronic irritation of mucous membranes is of great importance with regard to peripheral airway obstruction. Yet this has received virtually no attention although there is growing evidence that it can be produced in airways by a variety of agents.

Intercellular junctions are important determinants of cell function (16). The mechanism by which they act is only beginning to be unravelled. It is known that there are tight junctions both in the tracheobronchial mucosa and between type 1 alveolar cells. Whether or not abnormalities in these junctions are important in the pathogenesis of lung disease is unknown. However, it would seem that, in an organ continually exposed to inhaled particulates which are thought to be important in pathogenesis, the junctions must have a role in protecting the lung from injury.

Communications between cells (nexus) also exist in bronchial epithelium. It is postulated that these junctions are important in intercellular communication. There is evidence in the uterine cervix that these structures decrease in number as lesions progress from dysplasia to carcinoma in situ (17). Their role in metaplastic change in tracheobronchial mucosa is unknown but this would seem to be a fruitful area of future research.

Very little has been done in the area of cell turnover rates in the lung since the pioneering studies of Bertalanffy. The rate of turnover of type 1 and type 2 cells,and for that matter of bronchiolar cells, remains an open question, although it is quite conceivable that emphysema could result from a decreased rate of replacement of type 1 cells. If a valid method of measuring turnover rates were available, the influence of physiological, pharmacological and environmental factors on this would provide invaluable information.

Pathophysiology

The panel did not consider the chemical structure and function of the lung, even though this represents an area of research of great importance in emphysema, because this topic is addressed by another panel.

The pathophysiology of airways obstruction and emphysema in their advanced stages has been described in great detail from the point of view of lung mechanics, ventilation distribution, gas exchange, diffusion and pulmonary circulation. Suitable tests have been devised to readily detect airway obstruction when it is moderately advanced (18), and loss of elastic recoil, which is generally regarded as a hallmark of emphysema (19). Intelligent interpretation of routine function tests can be used to predict with a fair degree of certainty the presence, and indeed extent, of alveolar destruction in emphysema.

The control of ventilation is a subject of intense current research in physiological laboratories, but there is a need for studies with a clear cut application to disease. Methods have been devised to study the responses to CO_2 and hypoxia, but for application to patients these should be simple. The technology is currently adequate to test the CO_2 responsiveness. One method (20) of studying the immediate ventilatory response to hypoxia has the advantage of easy applicability, but it requires standardization and validation. For measurement of the output of the respiratory center, the most available promising technique is quantification of the electrical activity of the diaphragm, although again standardization of the methods and design, with systematic studies of sources of error are needed. Information is rapidly being developed on the mechanical properties of the respiratory muscles, their relationship to ventilatory control and their correlation with mechanical events of respiration. There is need for this type of study with quantitative and qualitative comparisons between normal subjects and patients with lung disease. In general it appears that basic studies have progressed out of proportion to clinical application. Application of the vastly accumulating body of knowledge of normal ventilatory control to the study of disease is an urgent requirement.

Closely related to the problem of ventilatory control and the development of respiratory failure, is the sensation of breathlessness. Very little that is new has developed in this area over the past decade (21). Because symptoms are subjective, the study of breathlessness is not subject to rigidly controlled scientific experiment. Encouragement of psychophysiological studies to quantify the patient's response to his disease might lead to important new symptomatic forms of therapy.

The relationship between structure and function in the lung has long been a subject of interest. With regard to airway disease, there appears to be a good correlation between the obstruction in peripheral airways and the lesions observed (4), although additional knowledge of the physiological consequences of specific components of the lesions, such as goblet cell metaplasia, inflammation, scarring, mucus plugs, etc., is needed to determine the contribution of each to the resulting disability. Although alveolar destruction is associated with loss of recoil, it is not known whether or not the mechanical abnormality precedes the breakdown of alveoli. The stress-strain characteristics of lung tissue are important in this regard, particularly the measurement of yield-stress. An aspect of structure-function interrelationships which was virtually ignored until very recently, but is currently receiving considerable interest, is the study of the distribution of stresses through lungs, and the parenchymal distortions that result from unequal stresses (22). Such studies are absolutely fundamental in order to determine the role, if any, that the mechanical stress plays in the breakdown of alveolar walls.

Pulmonary Defense Mechanisms

Research recommendations relative to these vital functions of the lung are discussed extensively in the report of another panel. They are applicable to all lung diseases.

If chronic bronchitis is a nonspecific response to inhaled irritants, the defense mechanisms of the airways are obviously highly relevant. Most studies on the deposition of particles have been theoretical (23) and there is a need to validate these models. The influences of physiological, pharmacological and pathological factors on deposition sites are virtually unstudied.

Closely associated with the problem of particle deposition is clearance both from the alveoli and airways. Although great advances in isotope techniques in the last few years have permitted study of deposition and clearance in man, existing methods are tedious, time-consuming and difficult to standardize. Deposition of aerosols is nonuniform in disease and occurs in different airways than in normal lungs. Studies to compare clearance rates in different diseases and subjects should employ methods which insure that deposition sites are the same. The few studies that have done so demonstrate that clearance is delayed in smokers and in some subjects following recovery from acute upper respiratory tract infections (24). Clearance from the whole tracheobronchial tree has been studied, but virtually nothing is known about clearance rates from airways of specific generations or size.

There is considerable need for improved technology in this area as well as for studies of interactions between clearance rates and physiological variables and pharmacologic agents; of the capacity of the tracheobronchial epithelium for regeneration; and of the viscoelastic and biochemical properties of mucus.

The alveolar macrophage has been receiving intensive investigation (25). In relation to the pathogenesis of emphysema, additional knowledge is needed about the ultra-structural and biochemical alterations in alveolar macrophages following exposure to physical, chemical and infectious agents. Questions to be answered are: Does release of proteolytic enzymes during phagocytosis play a role in the pathogenesis of emphysema? Do alterations in the metabolic functions of macrophages result in failure of their protective function, resulting in a predisposition to alveolar wall breakdown by environmental agents? What roles do surfactant and secretory immunoglobulins play in inactivation and detoxification? What are the factors which normally keep the tracheobronchial tree sterile, and how does their failure result in chronic colonization of the tracheobronchial mucosa with bacteria?

Apart from the skin, the respiratory tract is the organ most intimately exposed to the environment, and noxious environmental influences must first involve defense mechanisms. There is need for interdisciplinary research between environmental physiologists and those concerned with physiology, biochemistry and microbiology of lung defense mechanisms.

Models

It is extremely difficult to separate which of the pathophysiological abnormalities in patients are due to bronchitis and which are due to emphysema. For this reason patients with these disorders are usually stated to have "chronic obstructive pulmonary disease" or other similar all-encompassing names. While this serves to hide our ignorance, it scarcely advances knowledge of these diseases. This is a matter of more than academic interest. While there is general agreement that the possibility of restoring destroyed alveoli is remote, restoring the sterility of the tracheobronchial tree, reversing goblet cell metaplasia and inflammation in peripheral airways, and removing mucus from them would seem to be more realistic therapeutic goals.

A very promising approach to some of these questions is the use of *animal models* of "pure" chronic bronchitis and "pure" emphysema. Models are now available for both diseases. Under most intensive investigation, is that of emphysema induced by proteolytic enzymes (14). Papain is the enzyme most commonly employed, but knowledge is beginning to develop about the role of other enzymes, including endogenous ones found in leukocytes, macrophages, etc.

Investigation is needed on the physiologic, pharmacologic and environmental factors that affect proteolytic enzyme-induced emphysema, and particularly on the interrelationship between the mechanical stress to which the lungs are subjected and the breakdown of alveolar walls.

Animal models of bronchiolitis and "chronic bronchitis" have also been developed, but the pathophysiology of these models has not been extensively studied (26). Such models should prove extremely useful in determining the influence of physiological, microbiological, pharmacological and environmental factors in the etiology and pathogenesis of disease, in determining factors which protect against the abnormalities, and in identifying therapeutic measures designed to reverse them.

Mechanical, electrical and mathematical models of the lung have been used extensively in the past to provide qualitative insight into how the lungs behave. One of the most desirable features of such models is their behavior when a variable is manipulated in a manner that is not possible by biological experimentation. At least two aspects of the mechanical properties of lungs would seem ripe for such modelling: One is the maximum expiratory flow volume curve, which is potentially very useful as a diagnostic and possible prognostic test. Certainly other tests of lung function based on forced expirations have proven extremely useful in the past and the maximum expiratory flow volume curve is a more sensitive way of looking at this.

One of the problems with analysis of the curves, however, is that the normal range of shapes is large and the normal variability in maximum expiratory flow at specific lung volumes is not decreased by correcting for body size. In order to understand these normal curves and develop the test into a truly strong one, an adequate mechanical model is necessary. Although several have been proposed, none seem as yet adequate to understand the normal curve. If a reasonable model were available, it would also seem possible to evaluate other tests which may be closely related such as measurements of "closing volumes".

Another aspect of lung mechanics that requires modelling is the nonhomogeneous lung where the mechanical properties of different parts are nonuniform. Major contributions have been made to this problem (27), but little is known about how forces are distributed through the lung, how distortable lung tissue is, what internal stresses and strains are established by distortions, and whether they would be sufficiently great to lead to tissue breakdown. An engineering approach would seem inevitable if this model is to be accomplished. A possible approach might be through the study of distortions in isotropic metals.

Resources and Special Research Approaches

Manpower needs and availability must at present be estimated on the basis of professional judgments as reliable statistical data are not obtainable. Manpower with the necessary expertise is probably sufficient in such classical fields as the physiology of lung mechanics, ventilatory control and gas exchange, as well as in epidemiology. Engineers are now available as a consequence of the cutback in the space industry, but it is necessary to attract them to lung research where their role in lung modelling would be invaluable.

However there are other important fields in which few scientists in this country are currently working; for example, lung defense mechanisms. As research on lung defense mechanisms involves biochemistry, immunology, microbiology, environmental health and physiology, it is necessary that training be interdisciplinary and it is very desirable that the training be provided in more than one laboratory or institution. Interdisciplinary training is also needed to develop scientists competent to study both structure and function, and engineers knowledgable in biology, pulmonary physiology or any other field relevant to lung disease. Scientists and engineers with such interdisciplinary training could contribute to an understanding of how immunological, environmental, structural, microbiological, biochemical or other types of abnormalities might lead to abnormalities of function.

Strong consideration should also be given to training paramedical and technical personnel to assist in large epidemiologic studies or research that involves wide-scale screening of subjects or the accumulation of vast amounts of data.

Interdisciplinary research drawing upon the types of trained manpower noted above, is necessary for investigations into the early natural history of chronic obstructive lung disease, the definition of high risk groups, and the reversibility of pulmonary abnormalities. Such studies require cooperation among epidemiologists, physiologists and geneticists. Problems associated with cessation of smoking require cooperation between behavioral scientists and physiologists. To study animal models of human disease and the factors that may influence the disease process, physiologists must work closely with morphologists, pharmacologists, microbiologists, biochemists and immunologists. In the field of ventilatory control, cooperation is necessary between neurophysiologists and pulmonary physiologists. Interdisciplinary cooperation for mechanical and mathematical modelling of the lung and for studies of lung defense mechanisms have been mentioned. These examples could be multiplied but they are sufficient to emphasize the high priority that should be assigned to interdisciplinary research into nonallergic airways disease. A model interdisciplinary research center should be in the Intramural Lung Program of the National Heart and Lung Institute.

Cooperative studies that involve more than one laboratory and also more than one institution are necessary, particularly for long-term prospective studies to determine the early history of chronic bronchitis and emphysema; to define high risk groups; for assessing the efficacy of preventive interventions such as cessation of smoking and therapeutic interventions; and for validating, in more than one laboratory, diagnostic tests suitable for screening.

Technologic improvements that would be major contributions to research on diseases of airways include: (1) reliable noninvasive methods of distinguishing between the relative roles of reflexes, central mechanisms, chemoreceptor control, hypoxia and electrical activity of the diaphragm and other respiratory muscles in ventilatory control; (2) methods to study the biochemical composition and rates of secretion of mucus under different normal and abnormal conditions, and clearance rates at different levels of the tracheobronchial tree as such studies are important to an understanding of lung defense mechanisms; (3) techniques suitable for use in man that will be innocuous and make it possible to determine the exact pathway for alveolar-bronchiolar clearance; (4) valid techniques to study rates of cell turnover in alveoli and airways as these techniques are necessary in the study of etiology and pathogenesis of airways disease; (5) methods to determine whether airway narrowing or airway closure increases airway resistance, when and where true airway closure occurs in the lung, the degree to which mucus inflammation, obliteration and fibrosis contribute to airway obstruction, as such information is necessary for deciding where to direct therapeutic efforts.

CONCLUSIONS

I

It is known that chronic bronchitis and emphysema are irreversible by the time the patient presents with symptoms. It is essential to learn if early detection (when followed by appropriate therapeutic intervention) would reduce the incidence of these diseases and the disability from them.

In terms of ultimate control of nonallergic airways disease, research into early detection and reversibility at this stage is the area most likely to produce significant results in the shortest time and at the least cost.

Early diagnosis depends upon development of a simple reliable noninvasive test which can be widely applied to apparently healthy persons. The test must be able to detect peripheral airway obstruction in its early stage. While it must be sensitive, it must not be so sensitive as to detect subtle changes that are not prognostic of early disease.

A suitable test for early detection must be developed that is reliable, reproducible, sensitive enough to detect early disease, safe to perform, and simple and rapid enough to be performed on many persons a day.

A program of early diagnosis necessary to define groups at high risk of developing disease, and to determine the physiologic, genetic, environmental and structural basis of this risk. This requires cooperation among morphologists, geneticists, respiratory and environmental physiologists, and microbiologists.

Interlaboratory cooperation as well as interdisciplinary training and cooperation is necessary to assess the validity and usefulness of tests for early diagnosis and to study the structural, genetic and physiologic factors associated with high risk.

II

The difficulty of influencing the smoking habits of the general population is well known. It is equally well known that if it were possible to stop cigarette smoking the problems of chronic bronchitis and emphysema would largely disappear. Research is urgently needed into the psychophysiology of smoking and into methods -- be they psychological or pharmacological -- by which people can be persuaded not to smoke. Concomitant with this approach should be attempts to develop a "safe" cigarette although the possibility remains that chronic bronchitis is a nonspecific response to inhaled irritants and that no cigarette will be safe.

Biomedical scientists should work closely with psychologists on the problem of why people smoke, why they will not stop smoking even when convinced of the health hazards of the habit, and how such habits can be altered in large segments of the population.

Although research should eventually be carried out on developing a "safe" cigarette, immediate studies should be directed to the questions of whether chronic bronchitis is a nonspecific response to inhaled irritants.

III

Animal models of both emphysema and chronic bronchitis are now available, but are not being adequately exploited to study the pathogenesis and possible therapeutic regimens of these diseases.

Research is needed on animal models to determine etiologic factors associated with obstructive lung disease, mechanisms involved in the pathogenesis of chronic bronchitis and emphysema, and possible modes of therapy.

An understanding of the pathogenesis of chronic bronchitis and emphysema is essential to successful diagnosis, treatment and prevention. Fundamental to such an understanding is elucidation of the lung defense mechanisms, the general pathology of the lung, and how variables such as mechanical stress, pharmacological, biochemical and microbiological factors interact with one another. These mechanisms are very poorly understood at present; technologic development of new methods for research into fundamental problems is needed. If one can pinpoint how defense mechanisms fail and how the lung reacts to different insults, it may indicate the way to treatment.

Studies are needed on defense mechanisms and the general pathology of the lung under different physiological, biochemical, pathological and pharmacologic conditions and on clearance rates at different levels of the tracheobronchial tree.

IV

Although manpower requirements are met in some disciplines such as classical physiology, other disciplines necessary for fundamental studies in the pulmonary field are not sufficiently represented.

Training programs are needed to attract to pulmonary research individuals expert in relevant disciplines who can contribute to the advance of research on fundamental problems of lung diseases. Such training programs must be interdisciplinary.

V

Technological developments are necessary for basic advances in lung defense mechanisms, general pathology, ventilatory control and the relationship between structure and function.

Fundamental research should continue to be supported, particularly if it has promise of leading to technological breakthrough in an area where this is necessary.

RECOMMENDATIONS

I

INTERDISCIPLINARY INVESTIGATIONS, INVOLVING COOPERATION AMONG DIFFERENT LABORATORIES, SHOULD BE PROMOTED FOR THE LONG-TERM PROSPECTIVE STUDY OF POPULATIONS AT RISK FOR NON-ALLERGIC AIRWAYS DISEASE.

SUCH STUDIES SHOULD BE ADDRESSED TO QUESTIONS OF WHETHER THE DISEASE CAN BE DETECTED EARLY, WHETHER IT IS REVERSIBLE WHEN DETECTED EARLY, AND WHETHER THERAPEUTIC INTERVENTION HAS A BENEFICIAL EFFECT.

II

STUDIES ADDRESSED TO THE PROBLEM OF CIGARETTE SMOKING IN RELATION TO CHRONIC OBSTRUCTIVE LUNG DISEASE SHOULD BE ACTIVELY FOSTERED. RESEARCH SHOULD BE DIRECTED TO INTERVENTION BY BOTH PSYCHOLOGICAL AND PHARMACOLOGICAL MEANS, AND TO THE QUESTION OF WHETHER CHRONIC BRONCHITIS IS A NON-SPECIFIC RESPONSE TO INHALED IRRITANTS.

III

TO DRAW UPON NATIONAL MANPOWER RESOURCES THAT CAN CONTRIBUTE TO FUNDAMENTAL PULMONARY RESEARCH AND TECHNOLOGICAL ADVANCES, INTERDISCIPLINARY TRAINING PROGRAMS SHOULD BE FOSTERED. THEY SHOULD INCLUDE ENGINEERS, PHARMACOLOGISTS, GENETICISTS, MORPHOLOGISTS, MICROBIOLOGISTS, AND EPIDEMIOLOGISTS AS WELL AS PHYSIOLOGISTS, AND SHOULD NOT BE LIMITED TO PURELY "MISSION-ORIENTED" RESEARCH.

REFERENCES

1. Richler, F.C. and Woodward, E.G.: Survey of Professional Manpower in Pulmonary Diseases: Chest Disease Importance SRI Project, ECH-1316. Prepared for NTRDA. 1972.

2. Jones, N.L., Burrows, B., and Fletcher, C.M.: Serial Studies of 100 Patients With Chronic Airways Obstruction in London and Chicago. Thorax. 22: 327-335, 1967.

3. Woolcock, A.J., Vincent, N.J., and Macklem, P.T.: Frequency Dependence of Compliance as a Test for Obstruction in the Small Airways. J. Clin. Invest. 48: 1097-1106, 1969.

4. Hogg, J.C., Macklem, P.T., and Thurlbeck, W.M.: Site and Nature of Airway Obstruction in Chronic Obstructive Lung Disease. New Eng. J. Med. 278: 1355-1360, 1968.

5. Leblanc, P., Ruff, F., and Milic-Emili, J.: Effects of Age and Body Position on "Airway Closure" in Man. J. Appl. Physiol. 28: 448-451, 1970.

6. McCarthy, D.S., Spencer, R., Greene, R., and Milic-Emili, J.: Measurement of "Closing Volume" as a Simple and Sensitive Test for Early Detection of Small Airways Disease. Amer. J. Med. 42: 747-753, 1972.

7. Ingram, R.H. Jr. and O'Cain, C.F.: Frequency Dependence of Compliance in Apparently Healthy Smokers Versus Non-Smokers. In *Lung and Airways Mechanics in Normal Man and in Chronic Lung Diseases*, Entretiens de Physio-pathologie Respiratoire, ed. R. Peslin, Masson & Cie, Nancy, Paris . 1971.

8. Strieder, D.J. and Kazemi, H.: Hypoxemia in Young Asymptomatic Cigarette Smokers. Ann. Thorac. Surg. 4: 523-530, 1967.

9. Ito, H. and Aviado, D.M.: Presention of Pulmonary Emphysema in Rats by Progesterone. J. Pharmacol. Exp. Ther. 161: 197-204, 1968.

10. Macklem, P.T.: Obstruction in Small Airways - A Challenge to Medicine Am. J. Med. 52: 721-724, 1972.

11. Ingram, R.H., Miller, R.B., and Tate, L.A.,: Ventilatory Response to Carbon Dioxide and to Exercise in Relation to the Pathophysiologic Type of Chronic Obstructive Pulmonary Disease. Amer. Rev. Resp. Dis 105: 541-551, 1972.

12. Thurlbeck, W.M.: Chronic Obstructive Lung Disease In Pathology Annual. 3. ed. S.C. Sommers. Appleton-Century-Crofts. New York. pp. 367-398, 1968.

13. Reid, L.: Pathology of Chronic Bronchitis. Lancet. 266: 275-278, 1954.

14. Pushpakom, R., Hogg, J.C., Woolcock, A.J., Angus, A.E., Macklem, P.T., and Thurlbeck, W.M.: Experimental Papain-Induced Emphysema in Dogs. Amer. Rev. Resp. Dis. 102: 778-789, 1970.

15. Laurell, C.B. and Eriksson, S.: The Electrophorectic Alpha$_1$-Globulin Pattern of Serum Alpha$_1$ Antitrypsin Deficiency. Scand. J. Clin. Lab. Invest. 15: 132-140, 1963.

16. Weinstein, R.S. and McNutt, N.S.: Cell Junctions. Current Concepts. New Eng. J. Med. 286: 521-524, 1972.

17. McNutt, N.S., Hershberg, R.A. and Weinstein, R.S.: Further Observations on the Occurrence of Nexuses in Benign and Malignant Human Cervical Epithelium. J. Cell. Biol. 51: 805-825, 1971.

18. Butler, J., Caro, C.G., Alcala, R. and DuBois, A.B.: Physiological Factors Affecting Airway Resistance in Normal Subjects and in Patients with Obstructive Respiratory Disease. J. Clin. Invest. 39: 584-591, 1960.

19. Macklem, P.T. and Becklake, M.R.: The Relationship Between the Mechanical and Diffusing Properties of the Lung in Health and Disease. Amer. Rev. Resp. Dis. 87: 47-56, 1963.

20. Dejours, P., Labrousse, Y., Raynaud, J., Girard, J. and Teillac, A.: Stimulus Oxygene de la Ventilation au Repos et au Cours de 1' Exercise Musculaire a Basse Altitude (50m) chez 1 'Homme. Rev. Franc. Et. Clin. et Biol. 3: 105-123, 1958.

21. Porter, R.: Breathing. Hering-Breuer Centenary Ciba Symposium. Churchill, London. 1970.

22. Mead, J., Takishima, T. and Leith, D.: Stress Distribution in Lungs: A Model of Pulmonary Elasticity. J. Appl. Physiol. 28: 596-608, 1970.

23. Hatch, T.F.: Distribution and Deposition of Inhaled Particles in the Respiratory Tract: Conference on Airborne Infection. Bacteriol. Rev. 25: 237-240, 1961.

24. Lourenco, R.V., Klimek, M.F. and Borowski, C.J.: Deposition and Clearance of Two Micron Particles in the Tracheobronchial Tree of Normal Subjects-Smokers and Nonsmokers. J. Clin. Invest. 50: 1411-1420, 1971.

25. Cohen, A.B. and Cline, M.J.: The Human Alveolar Macrophage. Isolation, Cultivation In Vitro and Studies of Morphologic and Functional Characteristics. J. Clin. Invest. 50: 1390-1398, 1971.

26. Freeman, G., Crane, S.C., Stephens, R.J., and Furiosi, N.J.: Pathogenesis of the Nitrogen Dioxide-Induced Lesion in the Rat Lung. A Review and Presentation of New Observations. Amer. Rev. Resp. Dis. 98: 429-443, 1968.

27. Otis, A.B., McKerrow, C.M., Bartlett, R.A., Mead, J., McIlroy, M.B., Selverstone, N.J., and Radford, Jr.,E.P.: Mechanical Factors in the Distribution of Pulmonary Ventilation. J. Appl. Physiol. 8: 427-443, 1965.

PANEL IV

ALLERGIC AIRWAYS DISEASE: ASTHMA

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ALLERGIC AIRWAYS DISEASE: ASTHMA

INTRODUCTION

Asthma--more appropriately designated "chronic reversible obstructive airways disease"-- is defined as a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli, and made manifest by difficulty of breathing due to generalized narrowing of the airways. This narrowing is dynamic and changes in degree, either spontaneously or because of therapy. The basic defect appears to be an altered state of the host. It is well known that individuals with a history of asthma, or any atopic disease, usually show a raised sensitivity and increased reactivity to vasoactive amines. They react with bronchoconstriction, mucosal edema, hypersecretion of mucus and abnormal cellular infiltrates. Predisposing factors include: a genetic predisposition in some families; a local end-organ hypersensitivity to pharmacologic agents, irritants and specific allergens; and a special form of immunologic response, leading to the release of specific chemical mediators.

The panel concerned itself with the neuropharmacological and immunological aspects of the control of airways and the derangements which occur in asthma.

MAGNITUDE OF THE PROBLEM

Asthma is a remarkably common illness. Although the annual mortality is relatively small (4,000 deaths per year), the prevalence is high. Several surveys indicate that about four percent of Americans have active asthma, and an additional three percent have had it previously. It is as common in the young as in the old. It is a frequent cause of disability, being responsible for five percent of all chronic disabilities. In one year, it accounted for 85 million days of restricted activity, 33 million days in bed, and 5 million days lost from work. From a personal viewpoint, it is a particularly uncomfortable illness, and because of its chronic nature and variable course, it may last years, even a lifetime.

Asthma is a large burden on the health-care system. In 1968 there were 134,000 patients discharged from hospitals with a diagnosis of asthma-hay fever, with an average hospital stay of 8.3 days. In a recent year, 27 million patient visits were made to physicians because of asthma (1).

CURRENT STATE OF KNOWLEDGE

Natural History

The natural history of "asthma" is difficult to characterize since it is a heterogeneous syndrome; the natural history of the different asthmas is not known.

Longitudinal studies are needed to learn the genetic, pharmacological and immunological abnormalities in different "populations of asthmatics." It is generally believed that although asthma varies greatly from one patient to another, it tends to have fairly uniform patterns in any one patient.

If certain patients with hay fever are destined to develop asthma, it is important to identify them by longitudinal pulmonary studies before asthma develops, to determine whether its development can be prevented. Such studies would be facilitated by: nationwide computer-based medical records by unit number (to correct for mobile populations); and periodic evaluation of asthmatics in specific centers to identify changes in neuropharmacological and immunological variables.

Etiology

Recent awareness of new allergens in the environment has been associated with the discovery of new forms of asthma. For instance, industrial workers manufacturing detergents containing enzymes derived from Bacillus *subtilis* have shown a significant incidence of asthma, and similar cases have been found among housewives with lesser exposure (2). In this case, the antigen is known, but it is not known why some people who are exposed to it develop symptoms while others do not. Smoking, which exerts a deleterious effect on asthma (3), is probably the most widespread concentrated chronic source of air pollution and should be studied as an etiologic factor.

The role of infection in asthma must be clarified. Further detailed bacteriological and virological studies are needed to determine which bacteria and which viruses are associated with asthmatic attacks--probably not all are important. The role of infections in "setting the stage" for asthma is also important. Many patients appear to develop asthma *de novo* after a respiratory illness, but virtually nothing is known about the variables involved.

Pathogenesis

In people with the appropriate *immunologic* constitution, exposure to a variety of environmental antigens, both natural and artificial, leads to the production of a unique kind of immunoglobulin, IgE. Although this protein is found in small amounts in nonallergic people, it is present in larger amounts in patients with allergic asthma. It represents antibodies to the environmental antigens, and has the capacity to attach to certain cells (tissue mast cells or basophils) in the mucous membranes and skin. According to the mast cell theory of asthma, airborne antigen comes in contact with IgE cell-bound antibody at the surface of these cells. The antigen-antibody reaction causes the mast cell to release mediators, such as histamine and slow reacting substance of anaphylaxis (SRS-A), which travel short distances to act on smooth muscle, secretory mucous glands and blood vessels to produce bronchospasm, hypersecretion of mucus and edema (4). Chemotactic factors, which cause wandering inflammatory cells to accumulate, are also released.

Current research is addressed to determination of the exact chemical structure of IgE. The chemical nature of the mediators released is being investigated, and the role of intracellular cyclic AMP (C-AMP) is being studied since it may regulate the release of mediators. Inhibitors of mediator release, such as catecholamines and methylxanthines, show apparent synergism. Propranolol, which competes with catecholamines for the same receptors, is being studied in order to define the mechanism of action. Assay methods for mediator detection are being improved; the relative roles of the adrenergic and cholinergic systems are being studied; and methods are being devised to isolate basophils and mast cells.

The specific stereochemical requirements for the antigen and IgE interaction at the cell surface (which leads to mediator release) and what happens in antigen or antibody excess are not known. The cellular metabolic events underlying mediator release are obscure. Various hormones act on adenyl cyclase in different cells, but the precise nature of this interaction is not understood. Prostaglandins are a relatively new class of compounds which may influence adenyl cyclase activity but the mechanisms are unknown. Prostaglandins E_1 and E_2 may also inhibit histamine release by some receptor other than the β-receptor. This pathway needs elucidation.

The recent discovery of IgE structure and function has pushed immunological studies in asthma rapidly ahead. While advances have provided information pertaining to how antigens react with IgE to specifically trigger mediator release, there are also significant unsolved questions in this area: It must be established that allergens (for example, pollen dust antigens) deposit within the bronchial tree. There is information on deposition sites of aerosols that suggests that very little antigen of this particle size would enter the lung. Furthermore, if antigens do deposit in the bronchi, the processing and transportation of these substances across mucosal barriers to reach the mast cell surface must be elucidated. Finally, if antigen-antibody reaction at the mast cell surface causes the release of mediators, the detailed physiologic effects of these humoral agents must be clarified.

It has been apparent for a long time that there is a strong *genetic factor* involved in many cases of asthma. Monozygotic twins have a 19 percent concordance rate for asthma (5). It is not known whether they have inherited an increased ability to manufacture IgE, have an abnormality in either mast cell, histamine, acetylcholine, or SRS-A metabolism, or have inherited a mechanism causing partial blockage of the beta-adrenergic receptors. However, it is also important to look at the discordances: in 81 percent of twin pairs only one twin got asthma. Prospective studies of allergenic stimuli and of neuropharmacological mediators would be very worthwhile in these instances. What is the nature of genetic predisposition so prevalent in some families in which some or all members have asthma and hay fever or related disorders? Is there something abnormal in the way they handle antigens, particularly inhaled antigens?

Genetic links in antibody production have been recently identified in guinea pigs and in mice (6,7). These responses appear to be linked with genetic loci controlling histocompatibility gene products. Similar findings should be made in man if possible, by immunizing people of different genetic backgrounds with small doses of innocuous antigens. Local differences in end-organ sensitivity should be explored. Some patients have their nasal mucous membranes affected by allergy, some have the bronchi affected, while others have both.

Considerable knowledge exists about the *control of airways* in normal persons. The control is by a complex system which includes a normal "bronchial tone," mediated via vagal impulses (9). Central nervous system control is important in regulating depth and frequency of breathing, while adequate mucociliary clearance keeps the airways free of debris and infection. In asthma, the outstanding abnormality is a hyper-responsiveness of the bronchial tree to stimuli which are innocuous in non-asthmatics. Asthmatic lungs respond with bronchoconstriction to 1:100 to 1:1000 of the dose of histamine needed to produce bronchoconstriction in normal persons (10). This is a local organ hypersensitivity in asthma, since other organs and systems are not hypersensitive to histamine. Asthmatic lungs also hyperrespond to inhaled mecholyl, irritants such as dust, citric acid and to cold air, even when attacks are not present. Irritant nerve receptors have been identified in the respiratory epithelium. Although these are mechanoreceptors, they are also stimulated by histamine inhalation (9). This stimulation is blocked by isoproterenol.

The mechanism of hypersensitivity to agents such as histamine and mecholyl is under intense scrutiny. An animal model exists in which hypersensitivity to histamine can be induced in certain strains of mice by pertussis vaccine (8). The role of vagal influences in stimulation of irritant receptors is under study. It also now appears that while immunologically-induced bronchospasm can be prevented or ameliorated by adrenergic agents, this can also be accomplished by vagal interruption. This fact highlights the importance of the study of nervous reflex control of airways in addition to direct humoral mediator and immunologic control.

There is controversy about the abnormal hyper-responsiveness of asthmatic airways. Since there is clearly a genetic component in some families, a theory to account for this proposes that there is tendency toward chronic blockade of beta-adrenergic receptors in the lung (and perhaps elsewhere) (8). Others feel that induced changes in the ordinary control mechanisms and exaggeration of reflex responses are the problem.

The interrelations between the adrenergic and cholinergic systems in allergen-induced or irritant-induced bronchospasm are not understood. More must be learned about the neural receptors that are stimulated and chemical mediators that are released by allergens, histamine, mecholyl, dust, cold air, etc. Whether there are genetic defects in C-AMP metabolism or mediator

synthesis or release is not known. Chemical mediators such as histamine and SRS-A have been identified, but the roles of serotonin, bradykinin, the clotting system, and prostaglandins are poorly defined. Are mediators similar in all species? Which species are best to study? What are the finer mechanisms of neural reflex pathways controlling airway caliber in health and in asthma? Chemical mediators of airway reactivity, including histamine, bradykinin, prostaglandins, acetylcholine, SRS-A, etc., should be studied in order to understand their exact mode of action, their chemical receptors or target tissue, and means of blocking these. How does the release of one mediator influence others? Are different mediator systems activated by different insults such as allergens, nonspecific irritants, infection, exercise, etc.? What is the mechanism by which frequently used medications, such as corticosteroids, affect their synthesis, storage, release and target activity?

Neuropharmacological mechanisms should be further explored, preferably in man. Neural pathways and reflexes controlling airways resistance, particularly those mediated via the vagus, must be carefully worked out. Changes in irritant reflex pathways in normals and asthmatics should be studied, and the natural stimulation of these receptors and means of blocking them should be elucidated. The interrelations of nervous reflex arcs, release of mediators, inhibition of one mediator release by another and the biochemical targets of all mediators must be identified.

It is recognized that the central nervous system profoundly influences normal breathing mechanisms, and that "psychological factors," however vaguely defined, have definite effects on acute and chronic asthma. Recent advances in neurophysiology have identified neurotransmitter mechanisms within the CNS, and it is important to relate these mechanisms to control of the airways. The influence of CNS impulses on airway "tone" and reactivity to external stimuli should be studied. The neural and pharmacological pathways mediating exercise-induced bronchospasm are under investigation in man.

Behavioral dynamics in bronchial asthma have received intermittant attention for years. Attempts have been made to identify "asthma" personality types and reaction patterns. Little agreement has come out of these studies. In view of the complexity of such approaches and of the rapid advances currently being made on the immunologic and neurophysiologic level, it does not appear that large-scale or long-term behavioral studies have a great probability of success at the present time.

Better methods for measuring changes in airway caliber and resistance are being developed--"closing volume" techniques appear promising in disclosing early changes. Further work is being done to elucidate the actual site of airway narrowing in asthma. There is evidence to suggest person to person variation that may ultimately have important implications for therapy.

Host Defense

Pulmonary defense mechanisms, such as the self-cleansing features of the normal and diseased lung, should be studied further since it is not clear how different kinds of particles, including organic and inorganic dusts, etc., are cleared from airways. A rational basis for the development of expectorants and mucus thinners is badly needed since the immediate cause of death in severe asthma is mucus impaction. Most physicians agree that a really good expectorant (one that will liquify deep bronchial secretions and permit their expectoration) does not exist. Hypersecretion of mucus is recognized as a prominent component of asthma, but neither its mechanism nor its control are understood.

Respiratory secretions should be studied to elucidate their normal control, and the effects of various intrinsic and extrinsic modifiers (nervous, mediator, salt and water, temperature, etc.) The changes in rates of secretion, physiochemical characteristics, and biochemical constituents of sputum should be investigated, although it is not easy since this is a nonhomogeneous material.

Models

Asthma is primarily a spontaneous disease of man. This hinders controlled investigations; hence, there is a great need for a good model system. Better animal model systems are needed. The pertussis-sensitized mouse may be important biochemically but it has disadvantages from the pulmonary standpoint. It would be valuable to have strains of a larger animal (such as a guinea pig) which show genetic hyper-reactivity to mediators. All animal model systems below primates have the obvious disadvantage that their immunological systems, with regard to cytophilic antibodies like IgE, may be different from humans in important ways.

Therefore, primate models should be exploited despite their expense. Human IgE can be passively transferred to them and their mediators should be explored. They can be placed in controlled environments to explore variables in allergen exposure and in nonspecific stimuli. Their tissues can be tested in vitro.

Human model systems have advantages and disadvantages: On a cellular level, means of isolating relevant cells (e.g., basophils) from both blood and tissues should be improved. On an organ level, the use of normal human lung passively sensitized in vitro has been helpful. Perhaps cell culture lines can be used, depending on how well the differentiated properties of such cells remain. Lungs removed at surgery or at autopsy are appropriate for study. The continuing use of the whole human subject is essential for study for the full regulatory feedback machanism. Carefully controlled studies of normal and allergic patients exposed to allergens and nonspecific stimuli have already been started (11).

CONCLUSIONS

I

The tendency of asthma to occur in families underlines the importance of an understanding of the genetic factors involved in the etiology and pathogenesis of this group of diseases.

Studies are needed to identify the immunologic reaction patterns of persons who develop asthma, and to determine whether there are constitutional differences in pharmacologic reactivity.

II

Mechanisms involved in the control of airways in asthma are both complex and poorly understood. These mechanisms involve the interaction of neural pathways and pharmacologic mediators which are activated by immunologic and nonimmunologic triggers. Asthmatics show abnormalities in airways control which are not present in normal subjects. An understanding of these mechanisms is essential to effective treatment as well as prevention of asthma.

Significant advances will best result from a cooperative effort between physiologists, pharmacologists, and immunologists. While studies in man are essential, these studies could progress more rapidly if better animal models were available, thus permitting expansion of research in areas that would be inappropriate in patients.

III

The natural history of asthma is ill-defined. As asthma represents a heterogenous group of syndromes, it is necessary to know the natural history of all the different asthmas.

Longitudinal studies are needed to follow genetic, immunologic, pharmacologic and physiopathologic characteristics in different populations of asthmatics.

RECOMMENDATIONS

I

STUDIES OF ASTHMA SHOULD EMPHASIZE GENETIC FACTORS AND MECHANISMS OF AIRWAY CONTROL. SUCH STUDIES SHOULD DRAW UPON THE FUNDAMENTAL DISCIPLINES AND APPROACHES OF GENETICS, IMMUNOLOGY, PHYSIOLOGY AND PHARMACOLOGY, AND SHOULD EXPLOIT ANIMAL MODELS--PREFERABLY PRIMATES.

II

COOPERATIVE STUDIES TO ELUCIDATE THE ETIOLOGICAL FACTORS AND THE NATURAL HISTORY OF ASTHMA SHOULD BE FOSTERED.

REFERENCES

1. Davis, J.: NIAID Initiatives in Allergy Research. J. Allerg. 49: 323-328, 1972.

2. Franz, T., McMurrain, K.R., Brooks, S. and Bernstein, I.L.: Clinical Immunologic and Physiologic Observations in Factory Workers Exposed to B. subtilis Enzyme Dust. J. Allerg. 47: 170-180, 1971.

3. Sheldon, J.M., Lovell,R.G. and Mathews, K.P.: House Dust and Miscellaneous Allergens. In *A Manual of Clinical Allergy*, Saunders., Philadelphia. pp. 437-455, 1967.

4. Austen, K.R.: Histamine and Other Mediators of Allergic Reactions In *Immunological Diseases*. ed., M. Samter, Little Brown & Co., Boston. pp. 211-225, 1971.

5. Lubs, M. L. E.: Empiric Risks for Genetic Counseling in Families With Allergy. J. Pediat. 80: 26-31, 1969.

6. McDevitt, H.O. and Benacerraf, B.: Genetic Control of Specific Immune Responses. Adv. Immunol. 11: 31-75, 1969.

7. Vaz, N. and Levine, B.B.: Immune Responses of Inbred Mice to Repeated Low Doses of Ag: Relationship to Histocompatibility (H-2) Type. Science. 168: 852-854, 1970.

8. Szentivanyi, A.: The β-Adrenergic Theory of Atopic Abnormality in Bronchial Asthma. J. Allerg. 42: 203-232, 1968.

9. Nadel, J.A.: Mechanisms of Airway Response to Inhaled Substances. Arch. Environ. Health. 16: 171-174, 1968.

10. Curry, J.J.: The Action of Histamine of the Respiratory Tract in Normal and Asthmatic Subjects. J. Clin. Invest. 25: 785-791, 1946.

11. Itkin, I.H., Anand, S. Yau, M. and Middlebrook, G.: Quantitative Inhalation Challenge in Allergic Asthma. J. Allerg. 34: 97-106, 1963.

PANEL V

DIFFUSE PULMONARY FIBROSIS AND ACQUIRED CONNECTIVE TISSUE DISEASE

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DIFFUSE PULMONARY FIBROSIS AND ACQUIRED CONNECTIVE TISSUE DISEASE

INTRODUCTION

The panel addressed itself to the following diseases: idiopathic chronic diffuse interstitial pneumonitis; collagen diseases, more appropriately designated "acquired connective tissue disease"; and diffuse pneumonitis resulting from drug reactions and radiation fibrosis.

Specifically excluded from the panel's deliberations were: non-infectious granulomas (including sarcoidosis); occupationally-induced interstitial fibrosis; hypersensitivity pneumonitis; acute infectious pneumonitis; and acute respiratory distress syndromes. Most of these are covered in reports of other panels.

With the exception of diffuse pneumonitis resulting from radiation or drug reactions, all diseases considered by the panel are of unknown cause. Common to these widespread interstitial pulmonary diseases (1-4) are certain clinical and pathological features. The clinical pattern is associated with dyspnea, especially on exertion, with fine crepitant rales late in inspiration the most regular physical finding. In most instances, vital capacity and total lung capacity are reduced, but the maximum ventilatory capacity is well preserved. Both static and dynamic lung compliance are reduced and the work of breathing increased. In many but not all cases, disturbances of ventilation-perfusion relationships can be demonstrated.

The one most consistent finding, regardless of the technique by which it is measured, is significant reduction -- often to very low values -- of pulmonary diffusing capacity. In view of this general agreement among methods subject to diverse sources of error, it may safely be concluded that the syndrome is characterized by a defect in gas transfer. However, there is controversy as to whether this is the result of a defect in transfer through a thickened membrane, reduction in available surface area, or ventilation-perfusion inequality. In the views of some, reduction of diffusing capacity during exercise is the best indicator of diffuse interstitial disease. If diffusing capacity is normal, the appearance of some reticulation in the chest x-ray is unlikely to represent interstitial pneumonitis. But if the diffusing capacity is low and compliance reduced, a lung biopsy may be indicated, despite a normal chest x-ray (5).

Roentgenographic evidence may be very minimal or unrecognized early in the disease process. In more advanced disease, diffuse nodular densities and linear fibrosis, most marked at the bases, are the characteristic abnormalities. As fibrosis progresses, lung volume decreases.

Lung biopsies in diffuse interstitial pneumonitis can be accomplished without significant mortality or morbidity. The lung biopsy findings vary considerably with the stage of disease, from very early interstitial edema with lymphocytic infiltration, to extensive severe fibrotic distortion, commonly termed "honeycomb lung." These changes, as observed by the usual light microscopy, serve as an essential starting point to exclude sarcoidosis, silicosis, asbestosis, from the groups of diseases considered by the panel. Lung biopsy studies by light microscopy have been useful in classifying the various types of *idiopathic interstitial fibrosis*. But there is some controversy over the separation of the usual* and the desquamative interstitial pneumonia. There seems good reason to separate them because of the difference in response to prednisone. Desquamative interstitial pneumonia usually responds quite well while in usual interstitial pneumonia the benefits of prednisone therapy have been disappointing.

Acquired connective tissue diseases usually involve the bronchi and lungs, although the frequency of such involvement varies widely in the different diseases. *Rheumatoid arthritis* is the commonest of these diseases and the various forms of pulmonary changes have received considerable attention. Included among manifestations of the rheumatoid lung are pleurisy with or without effusion, multiple pulmonary nodules, rheumatoid pneumoconiosis or Caplan's syndrome, progressive interstitial fibrosis and pulmonary arteritis with pulmonary hypertension (6,7). The prevalence of the diffuse interstitial pulmonary fibrosis varies widely in reported series. In those patients with high rheumatoid factor titers, pulmonary involvement has been as high as 23 percent, but in the majority of reports it is difficult to be sure of the actual type of pulmonary involvement (8).

The differential diagnosis between the rheumatoid lung and the usual interstitial pulmonary fibrosis is frequently impossible from the lung biopsy alone. The use of immunofluorescent studies to demonstate large amounts of gamma M rheumatoid factor in the alveolar walls and pulmonary capillaries may be helpful although this has been reported in non-rheumatoid interstitial fibrosis (9). The high incidence of positive rheumatoid factor in patients with diffuse interstitial fibrosis without any evidence of rheumatoid arthritis has been well documented.

Systemic lupus erythematosus (SLE) is the second most common connective tissue disease. Pleural effusion is the most frequent form of pulmonary involvement, occurring in about one-half of patients (10). In a recent review of roentgenographic abnormalities in 111 patients with SLE, only 3 were believed to have a true lupus pneumonitis. Superimposed infections and uremic pulmonary changes were thought to be more frequent causes of the observed pulmonary abnormalities. However, other studies have shown that pulmonary function is frequently abnormal although the chest roentgenogram may appear normal (11). The abnormalities in pulmonary function were the same as those in the usual interstitial pneumonitis, where the lack of radiographic evidence is not unexpected. The lung biopsy itself is frequently not diagnostic, but the clinical picture and presence of anti-DNA antibodies are very useful in establishing the diagnosis (12).

* For the purposes of this report, idiopathic interstitial pneumonitis-fibrosis will be referred to as usual pneumonitis (or fibrosis).

Immunosuppressive drugs have been reported to be useful in SLE. While renal involvement has been treated more frequently, the diffuse interstitial lung lesion has also been reported to have improved with treatment (13). There is a growing body of evidence that immunologic reactions are involved in the pleural inflammation and pulmonary vascular reactions of systemic lupus. There is reason to believe that the changes in rheumatoid lung have a similar pathogenesis (14).

In *progressive systemic sclerosis* (scleroderma), although much less common than rheumatoid arthritis or lupus erythematosus, the lung is involved in almost all patients with this connective tissue disorder (15). The pulmonary function abnormality frequently precedes any roentgenographic evidence of the disease. Death from pulmonary scleroderma is common and ranks either second or third in frequency after cardiac and renal causes (16).

Sjogren's syndrome is a chronic connective tissue disease characterized by dry eyes, dry mouth, and frequently associated with rheumatoid arthritis, systemic lupus erythematosus, polyarteritis, polymyositis or scleroderma. Although Sjorgren's syndrome is a rare disease with the frequency of pulmonary involvement poorly documented, the immunological studies may be helpful in the understanding of tissue injury. *Polymyositis*, another rare disease, may be associated with severe interstitial pneumonitis. In both Sjogren's syndrome and polymyositis, the easily available tissue biopsies from the lip salivary gland in the former, and muscle biopsy in the latter, may allow development of immunofluorescent studies which are equally applicable to the lung (17). Necrotizing vasculitis (various forms of polyarteritis) and rheumatic fever are other connective tissue diseases that may involve bronchi and lungs.

Pulmonary changes in *reactions to drugs* are similar to, if not indistinguishable from, the type of tissue injury in the lung in idiopathic interstitial pneumonitis. Hydralazine hydrochloride induces a syndrome comparable to systemic lupus erythematosus. Other drugs that have been reported to produce a similar pattern include isoniazid, procainamide hydrochloride, and various anticonvulsive drugs. The pulmonary lesions occurring with hydralazine, busulfan and hexamethonium are those of a diffuse interstitial pneumonitis (18). Circulating antibodies to hydralazine and in vitro lymphocyte transformation to hydralazine have been demonstrated (19).

Radiation pneumonitis has been recognized for many years. The acute phase occurs 3 to 6 weeks after cessation of radiation therapy; the lowering of the pulmonary diffusing capacity is the most characteristic abnormality (20). Because of the present therapeutic approach to Hodgkin's disease with upper mantle radiation therapy, a reasonable number of patients without a significant pulmonary parenchymal abnormality and in whom base line pulmonary function tests can be obtained, are an excellent model for study. Of particular interest in the patients with Hodgkin's disease is associated derangement of cell mediated immune response which may be used as a model for immunological study in relation to the development of fibrotic response to radiation therapy. Pulmonary lesions are similar to those of interstitial pneumonitis.

It is noteworthy that the lung tissue responses leading to pulmonary fibrosis are similar to lung responses to injury from noxious agents, whether physical (radiation and radionucleotides), chemical (particles, vapors, metals which are toxic pollutants), or biological (infections). The lung tissue reacts in a rather consistent manner; pathogenetic mechanisms in the lung are rather limited.

MAGNITUDE OF THE PROBLEM

The incidence of the usual diffuse interstitial pneumonitis is not known. The disease is neither well recognized nor classified. However, the panel believes that it is not a rare disease and that in many areas of the country it exceeds the incidence of sarcoidosis and hypersensitivity pneumonitis. From a study of nontuberculous referrals, 951 (20%) of 4751 referrals from 1949 to 1971 had interstitial disease. Of the 951 cases of interstitial disease, 277 were classified as due to occupational or environmental factors. A reasonable estimate would be that 10 to 15 percent of the usual referrals to a pulmonary unit suffer from the usual diffuse interstitial pneumonia. In 1967, there were 1,614 deaths from respiratory disorders from collagen disease, and 4,218 from diffuse fibrosis. The incidence of some acquired connective tissue diseases is summarized below:

	Rheumatoid Arthritis	Systemic Lupus Erythematosus	Progressive Systemic Sclerosis
Cases per million population per year	500	30	12
Black to white ratio	1.5	4	1.5
Female to male ratio	2.5	7	3
Percent of cases diagnosed in childhood	5-10	5-10	1
Adult pattern	Increases with age	15-44 peak	Increases with age

CURRENT STATE OF KNOWLEDGE

Natural History

Very little is known about the natural history of the pulmonary component of these diseases. There appear to be periods of clinical remission and relapses in rheumatoid arthritis and lupus erythematosus, but no reliable information is available as to whether the usual interstitial pneumonitis is slowly progressive, or whether there are periods of stability followed by periods of recurrent lung damage. If relapses occur, it is important to know the factors that cause them. Clinical studies would emphasize the natural history of these diseases.

Essential to studies of natural history of a disease is its early recognition. The most reasonable method of recognizing the patient with early diffuse lung disease is through better identification of the earliest changes in the chest x-ray. Patients apparently showing radiographic changes should be studied clinically, including appropriate assessments of pulmonary function. If pulmonary function is sufficiently abnormal, lung biopsy should be considered.

Among impediments to early recognition are these: The very fine and diffuse nature of the early interstitial change makes the early roentgenographic recognition of these changes difficult. Pulmonary function tests available in most hospitals are only the simplest ventilatory studies, which are unlikely to provide evidence of early diffuse interstitial change. Many of the patients at highest risk of developing diffuse interstitial changes, i.e., those patients with the acquired connective tissue disease, are generally first seen by other subspecialty groups, such as rheumatologists, hematologists and dermatologists.

The most promising approach to identifying early evidence of the diffuse interstitial abnormality is to study patients accepted as being at highest risk. These include patients suffering from any of the acquired connective tissue diseases, especially rheumatoid arthritis, systemic lupus erythematosus and progressive systemic sclerosis.

Elucidation of the natural history of diffuse interstitial pneumonitis is important not only to obtain more information about the disease and its economic impact, but also to develop an appropriate therapy. In longitudinal studies the worsening patient can be identified and considered for controlled therapeutic studies with promising regimens.

Etiology

Clinical and morphologic features of usual interstitial pneumonitis appear sufficiently uniform to be thought to represent a disease entity resulting from more than one etiologic agent, possibly operating through a common mechanism. Immune injury is believed to play a central role, but genetic factors seem to modify susceptibility to, and expression of, the disease. Exogenous agents, including viral infections, some drugs, and radiation are also implicated as etiologic factors.

Immunologic responses have become of increasing interest in relation to various connective tissue disorders and the usual interstitial pneumonitides A high percentage of patients with diffuse interstitial lung disease have antinuclear as well as rheumatoid (gamma-globulin) factors. The majority of patients have immunoglobulins raised in a pattern similar to that in autoimmune diseases (8). It has been suggested (22) that T-lymphocytes (thymus-derived cells) play a vital role in preventing autoimmunity through two mechanisms. T-lymphocytes are normally unresponsive to autoantigens, and they do not cooperate in immune responses with B-lymphocytes (non-thymus derived cells) which produce antibodies in several situations. Virus infections can lead to T-cells sensitization and this could stimulate B-lymphocytes to produce autoantibody. There is evidence that T-cells also exert specific feedback control of autoantibody formation. Possible clinical examples are the presence of antinuclear antibodies in some cases of idiopathic pulmonary fibrosis with a history of preceding virus-like respiratory infection (22), and in patients treated with drugs (such as hydralazine) that may produce an interstitial pneumonitis.

That interstitial pneumonitis is an immunologic disease has led to the consideration of therapeutic reconstitution of normal cellular and humoral immune responses (23) with a variety of agents, including transfer factor -- a soluble material that appears to be devoid of adverse effects.

Genetic predisposition to various connective tissue diseases, especially systemic lupus erythematosus, is suggested by the tendency for it to occur in monozygotic twins and in families. Similarly, it has been established that relatives of patients with usual interstitial pneumonitis have a high risk of developing this disease (24). It is stated that the disease is transmitted as a simple autosomal Mendelian dominant factor; therefore the families of patients with interstitial pneumonitis should be carefully evaluated. Moreover, the mere fact that not all patients with Hodgkin's Disease who receive irradiation develop post-radiation fibrosis (25) is evidence of host factor differences. The challenging question is what factors are operative in influencing the development of a fibrotic reaction in about one-half of the patients while others with the same irradiation dose escape.

Some of the genetic factors influencing the development of pulmonary fibrosis may be elucidated through studies of HL-A (transplantation antigens) histocompatibility groupings in interstitial pneumonias, including those associated with acquired connective tissue disease. There appears to be considerable potential for elucidating the etiology as well as the pathogenesis of these diseases by histocompatibility studies (26,27). Studies in patients who develop a diffuse pulmonary lesion secondary to various drugs, such as hydralazine, hexomethonium, busulfan and nitrofurantoin, may furnish additional information as to the type of immunological injury that is produced as well as an opportunity to evaluate host variants.

Viral infections are of interest as etiologic agents that might alter the antigenic configuration of host cells (21) so that they become the target of autoimmune assault. Preliminary investigations suggest that viral agents may be associated with systemic lupus erythematosus. In New Zealand Black mice, which develop a syndrome similar to human lupus, a virus-like agent has been separated from lymphoma cells. Viruses are also implicated in the multisystem Aleutian mink disease.

Pathogenesis

An understanding of the development and course of pulmonary fibrosis can be advanced through elucidation of factors affecting collagen metabolism, especially its synthesis and degradation. This, in turn, may lead to specific intervention to prevent fibrosis. At some point in time, knowledge of collagen metabolism will approach a level where this ultimate aim will be attainable through either decreasing the synthesis of collagen, interfering with maturation of collagen, or by stimulating collagen degradation. However, from a biochemical and metabolic point of view, regulating collagen metabolism in the lung is a difficult task because of the slow turnover rate compared to that of collagen in other organs. Because of the diseased state, collagen synthesis in the lung is enhanced and a differential turnover rate of collagen in normal and affected tissue may favor the therapeutic effect on newly synthetized collagen. The unique structure of the lung with its communications with outer atmosphere could allow administering therapeutic agents in the form of an aerosol permitting a higher deposition of the drug in the lung.

In addition to factors controlling some specific steps of collagen metabolism, several other factors having rather nonspecific effects on the reactivity of connective tissue play an enormous role in the development of fibrotic lesions. Most discussed, but still poorly understood, are the genetic factors. The enormous inter-individual variability in connective tissue reactivity could be explained by the existence of various constitutional "mesenchymal" reactivity types, as suggested by several investigators. To prove this is a difficult but important task. To understand the meaning of individual reactivity reflected in great variations in the magnitude and dynamics of lung injuries, studies should be addressed to neurogenic, hormonal, enzymatic, mechanical and nutritional factors.

Models

A good animal for diffuse interstitial lung disease has been difficult to secure. Airway administration of various materials such as quartz dust, alone or mixed with various bacteria, lipid extracts of pneumonic lungs, mercury vapor, aerosolized cadmium sulfate, ozone, foreign antigen, and heterologous antilung serum have been utilized. Although these attempts have succeeded in producing interstitial lung damage, this damage has not evolved into a condition which closely resembles that in human disease.

Essential anatomic criteria for an animal model include: a mixed cellular exudate in the interstitium; protein exudate in air space, with or without leucocytes; proliferation of lining epithelium; gradual progression to fibrosis and honeycombing; continuing activity, even when partly fibrotic; and diffuse distribution with possibility of skip zones (28).

A late pulmonary lesion in Syrian golden hamsters caused by subcutaneously administrated N-nitroso-N-methylurethane has been noted to resemble fibrosing alveolitis in man (29). In an extension of these studies, lesions were produced by weekly subcutaneous injection of varying doses of the drug and were stopped at various times between 11 and 45 weeks (30). Development of the lesion resembled that of the usual interstitial pneumonitis or fibrosing alveolitis: It began as an acute alveolitis,often with hyaline membrane formation, and progressed through a stage of chronic interstitial inflammation to interstitial fibrosis and honeycombing and epithelial proliferation. The interstitial changes occurred only in the connective tissue part of the interalveolar septum; the capillary basement membrane was not thickened. In a later stage, there was a marked decrease of the alveolar capillaries, and damage to the alveolar epithelial cells was a prominent feature of the lesion. Repair of this damage appeared to involve the proliferation of type II epithelial cells. Later, the alveoli became lined by bronchiolar epithelium. Animals that were sacrificed 21 weeks to 18 months after cessation of injections still showed large areas of active involvement with alveolar shrinkage and dense inflammatory exudates.

Although there is species variation, the same type of lesions are now being developed in the dog. The dog appears less susceptible than the hamster, but was selected to test physiological changes which are difficult to study in the hamster.

This model should be explored in several species of animals including primates. The ease of production by subcutaneous injection rather than by the less easily controlled aerosol method makes this animal model the most promising one to explore. It is hoped that such a model would lend itself to serial physiological studies as well as to obtaining material for investigating immunological changes concurrent with or secondary to this type of pulmonary lesion.

Diagnosis

Lung biopsy material should be obtained on as many early lesions as feasible. The open thoracotomy has the advantage of obtaining a larger sample of tissue than the usual needle biopsy. However, in repeated biopsies the use of needle biopsy using a high speed air drill should be explored. The biopsy material should be cultured for fungi, tubercle bacilli, and especially for virus. Ultrastructure studies for changes compatible with virus infections would be of special importance. Although cultures for fungi and tubercle bacilli are of little importance in the usual interstitial pneumonitis, they are very important if an unexpected granuloma is encountered.

The serum levels of IgG, IgA, IgM, IgE, secretory IgA, rheumatoid factor, antinuclear factors and anti-DNA are useful. There is evidence that rheumatoid arthritis and systemic lupus erythematosus occur more frequently in patients with low IgA. All of these studies are helpful in an attempt to separate SLE and possible rheumatoid disease from the usual interstitial lung disease. Appropriate serological studies for viral infections should be considered if the clinical picture suggests any viral infection.

Immunologic studies of the patients should include: the newer in vitro methods relevant to cell mediated immunity, to show a relationship to any suspected antigen as well as viruses; attempts to identify autoantigens responsible for the disease, and serologic techniques, including immunofluorescence to look for antibodies. Evaluation of the subjects' immune factors as such, and of the number and competence of his various lymphocytes is feasible (31). Where biopsy material is available, immunofluorescence studies for antibodies and complement components in the lesions themselves are essential.

CONCLUSIONS

I

The natural history of diffuse fibrosis and acquired connective tissue diseases that involve the lung is poorly understood. Some etiologic agents have been identified -- viral infections, some drugs, and radiation -- but it is evident that host factors must play an important role. Not all persons exposed to agents causing lung damage develop these diseases. Genetic constitution and altered immunologic mechanisms seem to be risk factors.

Studies of the natural history of diffuse fibrosis and acquired connective tissue diseases are needed to identify risk factors. Special attention should be given to diseases whose cause is well identified. Such studies should include: detailed investigation of premortem morphology, using material obtained from lung biopsy; and immunologic and genetic assessments that draw upon the newest techniques.

II

The pathogenesis of these diseases is virtually unknown. Investigation of factors affecting collagen metabolism, and the development of animal models of human disease, are especially promising approaches.

Connective tissue metabolism should be investigated to learn more about neurogenic, humoral, enzymatic, mechanical and nutritional factors that cause alterations associated with both specific connective tissue diseases and the usual chronic interstitial lung diseases.

Animal models that are presently available should be intensively investigated, and new models should be developed that permit adequate serial assessment of pulmonary changes as well as of molecular and cellular alterations.

RECOMMENDATIONS

I

A COORDINATED EFFORT SHOULD BE DEVELOPED FOR LONGITUDINAL CLINICAL STUDIES TO IDENTIFY RISK FACTORS IN DIFFUSE FIBROSIS AND ACQUIRED CONNECTIVE DISEASES THAT INVOLVE THE LUNG. THIS EFFORT SHOULD HAVE ITS PRIMARY FOCUS IN CENTERS WITH LARGE NUMBERS OF PATIENTS AND SHOULD BE INTERDISCIPLINARY. FUNDAMENTAL DISCIPLINES SHOULD INCLUDE IMMUNOLOGY, GENETICS, ELECTRON MICROSCOPY, AND CONNECTIVE TISSUE BIOCHEMISTRY.

II

DISEASES OF WELL IDENTIFIED ETIOLOGY SHOULD BE EXPLOITED FOR STUDIES OF RISK FACTORS AND PATHOGENESIS. NEW ANIMAL MODELS SHOULD BE DEVELOPED THAT PERMIT SERIAL ASSESSMENT OF MOLECULAR, CELLULAR AND PHYSIOLOGIC PULMONARY CHANGES.

REFERENCES

1. Gaensler, E.A., Carrington, C.B. and Coutu, R.E.: Chronic Interstitial Pneumonias. Clin. Notes. Resp. Dis. 10: 3-16, 1972.

2. Spencer, H.: Chronic Interstitial Pneumonia. In *The Lung.* eds., A.A. Liebow and D.E. Smith. Williams and Wilkins, Baltimore. pp. 134-150, 1968.

3. Liebow, A.A.: New Concepts and Entities in Pulmonary Disease. In *The Lung.* eds., A.A. Liebow and D.E. Smith. Williams and Wilkins, Baltimore. pp. 332-365, 1968.

4. Dickie, H.A. and Rankin, J.: Interstitial Disease of the Lung - The Alveolar Capillary Block Syndrome. In *Clinical Cardiopulmonary Physiology.* ed., B.L. Gordon. Grune and Stratton, New York, 1960.

5. Bates, D.V., Macklem, P.T., Christie, R.V.: Diffuse Interstitial Fibrosis. In *Respiratory Function in Disease.* W.B. Saunders Company, Philadelphia. pp. 268-286, 1971.

6. Walker, W.C. and Wright, V.: Pulmonary Lesions and Rheumatoid Arthritis. Medicine 47: 501-520, 1968.

7. Markel, W., Abell, M.R., Mikkelson, W.M. and Whitehous, W.M.: Pulmonary and Pleural Lesions in Rheumatoid Disease. Radiology 90: 641-653, 1968.

8. McCombs, R.P.: Diseases Due to Immunologic Reactions in the Lung. New Eng. J. Med. 286: 1186-1194, 1972.

9. DeHoratius, R.S., Abruzzo, J.L. and Williams R.C. Jr.: Immunofluorescent and Immunologic Studies of Rheumatoid Lung. Arch. Inter. Med. 129: 441-446, 1972.

10. Dubois, E.L.: Lupus Erythematosus. New York Blakiston Division, McGraw-Hill, New York. 1966.

11. Bates, D.V., Macklem, P.T., and Christie, R.V.: Pulmonary Involvement in the Collagen Diseases In *Respiratory Function in Disease.* W.B. Saunders Company, Philadelphia. pp. 299-320, 1971.

12. Sharp, G.C.: Autoantibodies and Complement in SLE: A Reexamination. Hosp. Practice 6: 109-120, 1971.

13. Sperryn, P.N.: Systemic Lupus Erythematosus with Fibrosing Alveolitis. Proc. Roy. Soc. Med. 64: 58-59, 1971.

14. Hunder, G.G., McDuffie, F.C. and Hepper, N.C.: Pleural Fluid Complement in Systemic Lupus Erythematosus and Rheumatoid Arthritis. Ann. Intern. Med. 76: 347-363, 1972.

15. D'Angelo, W.A., Fries, J.F., Masi, A.T., and Shulman, L.E.: Pathologic Observations in Systemic Sclerosis (Scleroderma). Amer. J. Med. 46: 428-440, 1969.

16. Medsger, T.A., Masi, A.T., Rodnan, G.P., Benedek, T.G., and Robinson, H.: Survival with Systemic Sclerosis (Scleroderma). Ann. Intern. Med. 75: 369-376, 1971.

17. Cummings, N.A., Scholl, G.E., Asophy, R., Anderson, L.G., and Talal, N.: N.I.H. Conference: Sjogren's Syndrome:New Aspects of Research, Diagnosis and Therapy. Ann. Intern. Med. 75: 937-950, 1971.

18. Bates, D.V., Macklem, P.T., and Christie, R.V.: Pulmonary Function in Miscellaneous Conditions. In *Respiratory Function in Disease.* W.B. Saunders Company, Philadelphia. pp. 418-440, 1971.

19. Hahn, B.H., Sharp, G.C., Irvin, W.S., Kantor, O.S., Gardner, C.H., Bagby, M.K., Perry, H.M. Jr., and Osterland, C.K.: Immune Response to Hydralazine and Nuclear Antigens in Hydralazine Induced Lupus Erythematosus. Ann. Intern. Med. 76: 365-374, 1972.

20. Bates, D.V., Macklem, P.T., and Christie, R.V.: Response to Chemical and Physical Irritants. In *Respiratory Function in Disease.* W.B. Saunders Company, Philadelphia. pp. 361-400, 1971.

21. Allison, A.C., Denman, A.M. and Barnes R.D.: Cooperating and Controlling Function of Thymus Derived Lymphocytes in the Relation to Autoimmunity. Lancet 2: 135-140, 1971.

22. Nagaya, H. and Sieker, H.O.: Pathogenetic Mechanisms of Interstitial Fibrosis in Patients with Serum Antinuclear Factor. Amer. J. Med. 52: 51-62, 1972.

23. Lawrence, H.S.: Transfer Factor and Cellular Immune Deficiency Disease. New Eng. J. Med. 283: 411-419, 1970.

24. Bonanni, P.P., Frymoyer, J.W. and Jacox, R.F.: A Family Study of Idiopathic Pulmonary Fibrosis. A Possible Dysproteinemic and Genetically Determined Disease. Amer. J. Med. 39: 411-421, 1965.

25. Coulter, J.W., Ruth, W.E., and Kerby, G.R.: Pulmonary Complications in Mantle Field Irradiation in Hodgkin's Disease. American Thoracic Society Annual Meeting, Scientific Abstracts. 28, 1972.

26. Grumet, F.C., Camkell, A., Bodner, J.G., Bodner, W.F., and McDevitt, H.O.: Histocompatability (HL-A) Antigens Associated with Systemic Lupus Erythematosus. New Eng. J. Med. 285: 193-196, 1971.

27. Benacerraf, B. and McDevitt, H.O.: Histocompatibility Linked Immune Genes. Science,175: 273-279, 1972.

28. Carrington, C.B.: Organizing Interstitial Pneumonia. Definition of the Lesion and Attempts to Devise an Experimental Model. Yale J. Biol. Med. 40: 352-363, 1968.

29. Herrold, M.McD.: Fibrosing Alveolitis and Atypical Proliferative Lesions. Am. J. Path. 50: 639-651, 1967.

30. Ryan, S.F.: Experimental Fibrosing Alveolitis. Am. Rev. Resp. Dis. 105: 776-791, 1972.

31. Waksman, B.H.: Measurement of Cell Mediated Immunity. New Eng. J. Med. 286: 431-432, 1972.

PANEL VI

HYPERSENSITIVITY PNEUMONITIS

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HYPERSENSITIVITY PNEUMONITIS

INTRODUCTION

Hypersensitivity pneumonitis (extrinsic allergic alveolitis) is a diffuse interstitial granulomatous lung disease due to an allergic reaction following inhalation of a specific organic dust (1-3). Among the first antigens recognized as capable of producing this reaction were species of the mold Aspergillus. Many other antigens are suspected of producing similar reactions.

Immunogenic requirements and pathogenesis of this disease are incompletely understood, and diagnosis has depended upon a combination of clinical and laboratory criteria. The disease syndrome should be suspected in all patients with recurrent fever, chills, cough, and dyspnea; chronic unexplained cough, sputum production and dyspnea; and in patients with symptoms suggestive of chronic pulmonary fibrosis. Wheezing may occur but is unusual. The history may bring out a temporal relationship between exposure (occupation, hobby) and symptoms, but if the exposure is constant (contaminated home environments) the symptoms may be insidious and progressive.

In the typical acute form of hypersensitivity pneumonitis, episodes of fever, cough, and dyspnea occur 4 to 8 hours after exposure to the antigen. Characteristic but nonspecific functional abnormalities are decreased lung volume, carbon monoxide diffusing capacity and abnormal ventilation-perfusion ratio. Airway obstruction is exceptional. After a single exposure, the symptoms improve within hours to several weeks.

In its chronic form, the disease results from continuous or repeated exposure. Dyspnea may occur without fever but with weight loss and weakness; airway obstruction may be present in addition to the physiologic abnormalities mentioned above, and pulmonary fibrosis is often present.

Diagnosis of hypersensitivity pneumonitis rests on the association of a patient's pulmonary and/or systemic response with inhalation of an environmental dust. Chest roentgenogram features range from no abnormality to diffuse interstitial fibrosis. More common are bilateral nodular infiltrates and coarsening of bronchovascular markings. These latter features disappear with avoidance of exposure. Hilar adenopathy is rarely, if ever, seen. Although the roentgenographic and pulmonary function abnormalities are not specific, the majority of patients have serum precipitating antibodies against the specific offending antigenic dust (when it can be identified). However, these antibodies can also be detected in the serum of up to 40% of exposed, but presumably well, individuals (4).

The diagnosis may be proven by observing the patient for clinical changes following natural exposure to the environment containing the suspected organic dust. In selected cases, provocative challenge by controlled insufflation may be indicated.

Many of the clinical features of the illness disappear when the offending dust is avoided, but in some patients pulmonary symptoms persist despite prolonged avoidance of exposure.

Some forms of infiltrative pulmonary disease characterized by restrictive or obstructive pulmonary dysfunction may overlap with hypersensitivity pneumonitis as defined above. These include the following:

- -Allergic bronchopulmonary Aspergillosis. In spite of primary obstructive dysfunction, these patients present with evidence of infiltrative pulmonary disease (5,6).
- -Pulmonary manifestations of hypersensitivity vasculitis, "rheumatoid lung," lupus erythematosis, polyarteritis, and other likely hypersensitivity pneumonitides associated with administration of certain drugs (e.g., hexamethonium, nitrofurantoin).
- -Certain "idiopathic" pulmonary diseases with or without associated systemic involvement (currently categorized as possible sarcoidosis), interstitial pneumonia or "idiopathic" pulmonary fibrosis.

MAGNITUDE OF THE PROBLEM

Hypersensitivity pneumonitis is not categorized in statistical reports of incidence of respiratory diseases. Patients with this disease may be included under inhalation diseases, interstitial diseases, or even diseases of the airways, because of presenting symptomatology. Nevertheless, some data are available on specific forms of hypersensitivity pneumonitis.

Several estimates are available on the frequency of *farmer's lung*. A collaborative study in 1964 reported that of 311 farmers with respiratory symptoms, 41 had precipitins to moldy hay. The patients came from Pennsylvania, Indiana, Illinois, North Dakota, Manitoba, New York and Wisconsin (7). An additional 63 cases were identified in Northern New York (8). In one county in Scotland (9), 7.8 cases per 100,000 were found in the general population, but among farmers the frequency was 110 per 100,000.

In the past 10 years, over 200 cases of farmer's lung have been seen at a university center and another 200 at a large clinic in Wisconsin. Referrals have greatly declined in frequency in recent years as primary physicians have become familiar with diagnosis and treatment of the disease. Patients are now treated at home rather than referred to university hospitals. One referral clinic still sees about 20 new patients a year, a frequency about the same as new cases of sarcoid.

Over 600 cases of *bagassosis* are referred to in the literature, and of these approximately 500 are in Louisiana. The disease is of worldwide distribution and occurs wherever sugar cane is processed, having been reported from Louisiana, Texas, Missouri, Illinois, Puerto Rico, India, Cuba, Italy, England, Peru and other areas. Several cases have been seen in non-occupationally exposed individuals, such as persons using the material as a garden mulch, housewives residing in homes several miles downwind from sugar cane fields and processing areas, and employees working in air-conditioned offices at or near sugar cane processing areas.

It is noteworthy that following an outbreak of *maple bark stripper's disease,* changes were made in the operations of the paper mill and no new cases occurred. This underlines the public health value of recognition of a disease and identification of offending antigens. Industrial outbreaks can be controlled by proper manufacturing processes.

A study of a recent outbreak of a hypersensitivity pneumonitis occurring in an office contaminated with *thermophilic actinomycetes* (7), where all individuals were apparently exposed to the same amount of antigen and were subsequently examined, revealed that: of 27 individuals, 4 had proven hypersensitivity pneumonitis (2 had the acute form, 2 subacute); 8 had precipitins against the offending antigen but were clinically well; and 15 had no clinical or laboratory evidence of the effects of exposure. These figures indicate that whereas 15% of the exposed group became ill, an additional 35% developed precipitins without detectable illness.

Those who have had experience with hypersensitivity pneumonitis are convinced that the diagnosis is being missed and that it is more common than published figures would imply. The frequency of hypersensitivity pneumonitis due to antigens which have not as yet been identified is very difficult to estimate. Referral centers interested in hypersensitivity pneumonitis see about 6-8 cases a year which might be due to unidentified antigens. When index cases have been found, survey of persons similarly exposed has usually identified additional previously unrecognized cases.

Although no definite statistics are available for deaths due to hypersensitivity pneumonitis, it is fair to say that morbidity rather than mortality is the major problem. However, deaths do occur: at least 8 deaths due to farmer's lung have been reported, and 4 deaths due to bagassosis.

In bagassosis the morbidity is high, perhaps because of the intensity of the occupational exposure. Patients are often incapacitated due to pulmonary disability for 6 to 18 months after an acute episode; hospitalization is usually necessary for at least a month; and a significant number of patients progress to chronic restrictive and/or obstructive lung disease without full recovery. Furthermore, severe financial, family and domestic problems result from the fact that these patients can never return to their primary work environment and must be occupationally rehabilitated at considerable cost to the community as well as to the individual involved.

Overall, sequelae and complications of hypersensitivity pneumonitis appear to be those associated with chronic lung disease. These progressive physiologic and structural abnormalities result in the inability of the patient to function in his daily activities, and thus increase the need for hospitalization and out-patient medical care in such individuals.

CURRENT STATE OF KNOWLEDGE

Natural History

Relatively little is known about the natural history of hypersensitivity pneumonitis; most of the information available is for two varieties of the disease: farmer's lung and pigeon breeder's disease. Among 50 patients with farmer's lung followed for up to 6 years, there were 5 deaths, presumably due to complications of progressive respiratory disease. The morbidity rate in this series was 30%, with pulmonary disability due to fibrosis being the major problem. In pigeon breeders, the course of disease may be more variable. Ten patients followed for five years revealed that either fibrosis with "stiff lung" or bronchiolitis obliterans with irreversible emphysematous changes may develop. Avoidance of exposure, however, usually brings about reversibility of the abnormalities, if structural changes have not occurred in the lung.

To advance knowledge of the natural history of hypersensitivity pneumonitis, it is necessary to develop more specific screening tests, such as skin tests with purified antigens, gel diffusion studies, and pulmonary function and x-ray examinations of populations at risk. To assess more precisely the possible differences in effects of long-term exposure or avoidance of various antigens, long-term follow-up is needed of known cases with different etiologies.

Recognition of hypersensitivity pneumonitis as a distinct entity depends upon identification of the causative antigens. Several have been recognized, many others are suspected, and specific precipitating antibodies have been found in the sera of appropriate patients. The role of precipitins in the pathogenesis of these diseases is uncertain, but the diagnostic importance of their association with disease is generally recognized.

Demonstration of precipitins depends upon isolation of the specific antigen and the demonstration of antibody by immunologic techniques such as immunodiffusion. With the advent of commercial agar gel diffusion kits for demonstration of serum anti-actinomycete, fungal and organic dust precipitins, there is now a clear need for standardization of antigens and techniques employed. However, it is important to emphasize that: serum precipitins may be absent when the disease is not in an acute phase; some asymptomatic individuals may develop precipitins without overt hypersensitivity pneumonitis; and false negative tests are frequent, usually because antigens are of insufficient potency and purity. It should also be noted that: gel diffusion techniques have limitations; there is need for proper antigen-antibody concentration ratios, and for washing and protein staining; and several types of false positive precipitin arcs exist.

The antigens presently recognized as causing hypersensitivity pneumonitis are encountered in organic dusts with particles of about 1 to 5μ. For sensitization heavy exposures may be required but reexposure to small amounts may provoke symptoms in sensitized persons. However, the occurrence of disease in parakeet owners or pituitary snuff takers implies that occasionally continuous exposure to a small amount of antigen may also sensitize. Usually when one patient has been identified as suffering from hypersensitivity pneumonitis to some antigen, a survey of individuals in the same or in identical environments discloses additional cases.

For screening purposes a suspected dust should be checked for antigen content. Controls should include sera of healthy nonexposed persons and persons similarly exposed but not ill. If precipitins are present in affected persons and in some of those exposed but not affected, but are absent in persons who were not exposed, the crude extract is assumed to have the antigen. Further identification requires culture of the dust for thermophilic and mesophilic molds and bacteria and preparation of antigens from these microorganisms. The dust should also be examined for presence of insects and mites, and suitable antigens prepared from the arthropods. Recent recognition of hypersensitivity pneumonitis due to thermophilic actinomycetes growing in air-conditioners (20) and humidifiers (21) indicates that, even if no obvious source of dust exists, the patient's environment should be cultured for a variety of microorganisms and extracts prepared from the predominating organisms. Precipitins are now being detected against many organic dusts, danders and fungal antigens in various percentages of the normal population with the use of more sensitive tests such as counter-immunoelectrophoresis (22).

Final identification rests on close observation of the patient following return to the suspected environment during an asymptomatic period, and, if necessary, specific provocation of symptoms following aerosol challenge with the purified and identified antigen. Provocative challenge is not without hazard and cannot be recommended as a routine procedure. Considerably more work is needed to standardize and evaluate the place of provocative challenge in the diagnosis of these diseases.

Pathogenesis

Potential antigens of almost infinite number and variety are inhaled into the lungs during a lifetime, but apparently only certain ones are capable of eliciting immune responses under certain circumstances, with subsequent participation in hypersensitivity reactions involving the airways and/or lung parenchyma. The lung defends itself and the body from inhaled materials by various means, but very little is known of the role played by immunological mechanisms in this defense. To what extent these mechanisms are protective, to what extent destructive, and what factors determine these alternatives require elucidation. As clinical hypersensitivity pneumonitis is produced by the inhalation of mold spores and organic dusts, it presumably exemplifies immunological mechanisms which are destructive.

Little is known regarding conditions required to stimulate an immune response to inhaled antigen. The immune response to injected antigen is heterogeneous, involving several classes of immunoglobulins with different biological properties, as well as sensitized lymphocytes which release multiple soluble factors upon antigen challenge. The role of cell-mediated (delayed) hypersensitivity in hypersensitivity pneumonia is presently unknown, but appears to account for acute lesions in experimental animals bearing histopathological resemblances to the spontaneous disease in man (10,11).

Evidence does exist that the respiratory tract may function as an immunologic organ in response to antigenic stimulation. It may respond to infectious agents with secretory immunoglobulin responses and specific cellular responses (12,13). Anatomical divisions of the respiratory tract, such as the trachea, have been shown to mount immunologic responses to soluble protein and infectious antigens (14,15). The production of secretory IgA antibodies in the respiratory tract has been recognized, and evidence is mounting that IgM and IgG antibodies may be produced by the lung against antigens entering the lower respiratory tract. IgE antibodies may be produced locally under experimental conditions and may be related to intensity of respiratory reactivity to the antigen.

The relationship of local respiratory immune response to human disease states is an area of great potential importance. That local immunologic reactivity of the lung may participate in the development of infiltrative hypersensitivity pulmonary disease is suggested by the finding that an elevated IgE level, at times dramatic, may be associated with the presence of Aspergillus fumigatus in patients with bronchopulmonary allergic aspergillosis (16). Additional search for such relationships in this and other hypersensitivity pneumonitides might provide meaningful correlations between local immune responsiveness and human disease. However, there are inherent difficulties in gathering information about human disease, such as the problems of collecting and standardizing samples from patients and the limitations of obtaining material from human lung by invasive techniques.

The immunologic mechanisms responsible for tissue injury are perhaps best studied in animal models (10,11,17,18). Pulmonary lesions of various types can be produced by exposure of previously sensitized animals to antigen aerosols. Selective active and/or passive immunization allows evaluation of the roles of specific antibody, cells, and mediators. Little has been learned as yet about the handling of inhaled antigen and the subsequent development and versatility of the immune response in experimental animals. Fog-fever in cattle and "broken-wind" in horses are spontaneous diseases which have been inadequately exploited, and may be helpful in elucidating pathogenesis in human respiratory diseases including the hypersensitivity pneumonitides.

Pathological anatomy of the pulmonary parenchyma in farmer's lung has been well studied with light microscopy and standard techniques of tissue preparation (19). Little information is available on specialized

techniques such as electron microscopy and immunofluorescence. Since precipitating antibody to recognized antigen is the immunological hallmark of this category of diseases, it has been assumed that hypersensitivity pneumonitis is a localized Arthus (or Type III) hypersensitivity reaction (1). The role of precipitins in pathogenesis is uncertain, however, and may be simply an accompanying rather than causative phenomenon.

Host Factors

The role of host factors in the etiology, severity or progression of hypersensitivity diseases warrants further study. Information is so limited that it is only possible to speculate about their contribution.

Age might seem to be an important host factor because the great majority of cases of hypersensitivity lung disease have been reported in adults. But this might be less a matter of age per se than the fact that these diseases are most likely to occur from occupational exposure in farmers and industrial workers; that they are probably potentiated by smoking and exposure to other irritants; and that alterations in the quality of immunologic responses with age may contribute to increased hypersensitivity.

An example of the changing quality of immunologic response is the decline in onset of IgE-mediated disease with age. While this is not postulated as a mechanism of hypersensitivity pneumonitis, changes in immunologic responsiveness of other types may account for increasing pulmonary hypersensitivity diseases with age. Possible mechanisms here may be theoretically similar to those which occur with drug reactions in which a combination of exposure and host factors may result in an increase in the older population.

That hypersensitivity pneumonitis is not restricted to adults is demonstrated by reports of pulmonary allergic aspergillosis and pigeon breeder's disease in children.

Genetic factors control the immunologic responses of an organism and therefore are implicated in hypersensitivity responses. The role of genetic control of immunologic factors in hypersensitivity lung disease is complex and speculative, but some examples of such interrelationships are available.

A combination of IgE, IgG,and possibly cell-mediated hypersensitivity responses,appear to contribute to development of pulmonary allergic aspergillosis. The IgE response, which is by far the more restricted response in the general population, precedes and contributes to the reaction in pulmonary allergic aspergillosis.

The IgG and cell-mediated responses occur more widely in population groups and are important individually or in combination in other hypersensitivity lung diseases, including farmer's lung.

In such diseases as farmer's lung, a variety of genetically controlled immunologic responses may participate in induction, severity and progression of the disease. Such responses may be genetically involved in the humoral antibody system by affecting the subclasses of IgG antibodies that are produced, the degree of antibody response to a given stimulus, or the relationship of the secretory immune system to the hypersensitivity lung diseases. It is possible that an IgA response of the respiratory secretory immune system may be significantly protective and that hypersensitivity lung disease might be more severe or more progressive in subjects with deficiencies of the secretory IgA system.

It is possible that non-immunologic factors may also contribute to hypersensitivity lung disease on a genetic basis. Their role is still speculative, but such factors may, in combination with immunologic mechanisms, interact to mutually contribute to production of allergic lung disease.

Environmental Factors

Geography in relation to occupation is important in bagassosis, and is probably important in the incidence of farmer's lung in Wisconsin. The newly recognized hypersensitivity lung diseases associated with contaminated humidifiers (21) might be expected to be related to geography (northern climates) and season (winter). Disease associated with contaminated air conditioning (20) might be related to season, economic status and occupation as well as geography.

Toxic factors might contribute to the induction, progression and severity of hypersensitivity lung disease, but these factors have not been adequately assessed. Possibilities to be investigated are chronic inhalation of tobacco smoke, air pollution, and industrial exposures to irritants, simple chemicals acting as haptens, and coal dust. Possible mechanisms of potentiation by these factors include increased absorption of antigens as a result of inflammatory reactions in pulmonary tissue, and increased immune responses locally, systemically, or both, as a result of an "irritant adjuvant" effect.

Infections as factors in infiltrative hypersensitivity lung disease have not been adequately studied. Two possibilities are that:

- a significant part of disease due to certain microbial agents might be the result of immunologic hypersensitivity reactions in which the infectious agent or its components contribute as antigens, or
- infectious agents might contribute to the induction, severity or progression of hypersensitivity lung disease by means of stimulation of the immune response by adjuvant action, enhancement of absorption of macromolecules through inflamed mucosal surfaces, or by other nonspecific mechanisms.

Handling of infectious agents by the lung is obviously accompanied by a variety of responses: neutralizing or destroying the agent, inflammation, injury to host tissue, fibrosis and healing. The balance among these responses is complex and poorly understood. Some infections may lead to permanent damage or to a self-perpetuating lesion resembling a hypersensitivity pneumonitis, while others initiate massive inflammation and then heal completely. Factors responsible for these differences require elucidation as there is no evidence either for or against infections having a role in hypersensitivity lung diseases.

CONCLUSIONS

I

The basic mechanisms that underlie the development of pulmonary hypersensitivity diseases following inhalation of antigens are not understood. At present recurrent attacks can only be prevented by avoidance of exposure to specific antigens. Neither prevention nor effective treatment can be achieved until the pathogenesis of these diseases is elucidated.

While many antigens causing hypersensitivity pneumonitis have been identified, the factors and events required for an immunogenic response, and the mechanism by which pulmonary lesions are produced, are still unknown.

Because of obvious difficulties in extensively studying humans, the most promising approach to an understanding of the pathogenesis of hypersensitivity pneumonitis is through animal models. Elucidation of pathogenic mechanisms in animal models may contribute to the development of more consistently reliable tests for diagnosis of hypersensitivity pneumonitis.

Basic problems that should be addressed include mechanisms by which inhaled antigens produce an immunogenic response; the roles of humoral and cellular mechanisms in the production of various pulmonary lesions; and the effects of immunoglobulin class and biological activity on hypersensitivity reactions.

II

There is mounting evidence that antigens presently unsuspected may be involved in hypersensitivity pneumonitis. Identification of precipitating antibody to isolated antigenic material is essential to the diagnosis of these hypersensitivity lung diseases. Procedures are available for screening suspected dusts for antigen content, but final identification rests on close observation of the patient when exposed to the suspected environment, and in some instances provocative challenge by the antigen is necessary for definitive diagnosis.

Studies are needed to explore the adaptability of more sensitive uncomplicated gel diffusion techniques, such as counter-immunoelectrophoresis, to demonstrate serum precipitins, particularly for identification of new antigens.

Standardization is necessary to permit comparison on a national basis of antigen sources for gel double diffusion studies. Such standardized preparations are necessary to evaluate the role of provocative challenge in the diagnosis of hypersensitivity pneumonitis.

III

Studies on the natural history of hypersensitivity pneumonitis are necessary for more effective diagnosis and treatment of these diseases.

Long-term follow-up studies of known cases with different etiologies are necessary to assess the effects of long-term exposure to, or avoidance of, various antigens. These studies are also necessary to develop more specific and more sensitive screening tests as well as to characterize the immune mechanism involved in the perpetuation of, or recovery from, these diseases.

RECOMMENDATIONS

I

RESEARCH ON HYPERSENSITIVITY PNEUMONITIS SHOULD EMPHASIZE MULTIDISCIPLINARY STUDIES OF PATHOGENESIS. APPROACHES SHOULD INCLUDE EPIDEMIOLOGIC STUDIES WITH FOLLOW-UP OF CASES WITH DIFFERENT ETIOLOGIES, AS WELL AS STUDIES OF HOST FACTORS.

II

ANIMAL MODELS SHOULD BE FULLY UTILIZED FOR INTERDISCIPLINARY STUDIES TO ELUCIDATE BASIC IMMUNOGENIC AND PATHOGENIC MECHANISMS OF LUNG INJURY BY HYPERSENSITIVITY REACTIONS.

III

COOPERATIVE STUDIES SHOULD BE FOSTERED TO STANDARDIZE ANTIGENS AND THE TECHNIQUES USED IN DIAGNOSIS AND CLINICAL INVESTIGATION OF HYPERSENSITIVITY PNEUMONITIS.

REFERENCES

1. Pepys, J.: Hypersensitivity Diseases of the Lungs Due to Fungi and Organic Dusts, Monographs in Allergy. 4, S. Karger Inc., New York, 1969.

2. Reed, C.E., Sosman, A., and Barbee, R.A.: Pigeon-Breeder's Lung: A Newly Observed Interstitial Pulmonary Disease. JAMA. 193: 261-265, 1965.

3. Salvaggio, J., Arquembourg, P., Seabury, J., and Buechner, H.: Bagassosis: IV. Precipitins Against Extracts of Thermophilic Actinomycetes in Patients with Bagassosis. Am. J. Med. 46: 538-544, 1969.

4. Fink, J.N., Sosman, A.J., Salvaggio, J.E., and Barboriak, J.J.: Precipitins and the Diagnosis of a Hypersensitivity Pneumonitis. J. Allerg. Clin. Immun. 48: 179-181, 1971.

5. Golbert, T.M., and Patterson, R.: Pulmonary Allergic Aspergillosis. Ann. Intern. Med. 72: 395-403, 1970.

6. McCarthy, I.S., and Pepys, J.: Allergic Bronchopulmonary Aspergillosis. Clinical Immunology (1) Clinical Features, and (2) Skin, Nasal and Bronchial Tests. Clin. Allerg. 1: 261-286, 415-432, 1971.

7. Wilson, J.R.: Farmer's Lung. New York J. Med. 65: 3013-3015, 1965.

8. Constantine, J.M.: Farmer's Lung as Observed in Chest Survey Clinics. New York J. Med. 65: 3015-3020, 1965.

9. Body, D.H.A., The Incidence of Farmer's Lung in Caithness. Scot. Med. J. 16: 261-262, 1971.

10. Richerson, H.B.: Acute Experimental Hypersensitivity Pneumonitis in the Guinea Pig. J. Lab and Clin. Med. 79: 745-757, 1972.

11. Miyamoto, T., and Kabe, J.: The Lungs as the Site of Delayed-Type Hypersensitivity Reactions in Guinea Pigs. J. Allerg. 47: 181-185, 1971.

12. Waldman, R.H., Mann, J.J., and Kasel, J.A.: Influenza Virus Neutralizing Antibody in Human Respiratory Secretions. J. Immun. 100: 80-85, 1968.

13. Waldman, R.H., and Henney, C.J.: Cell Mediated Immunity and Antibody Responses in the Respiratory Tract After Local and Systemic Immunization. J. Exp. Med. 134: 482-494, 1971.

14. Lieberman, P., Patterson, R., Peterson, V., Chakrin, L.W., Wardell, J.R., and Ricks, J.: Effect of Antigen Variation of Production of Antibody in Canine Tracheal Secretions. J. Immun. 107: 1349-1356, 1970.

15. Lieberman, P., Berlin, B.S., Metzgar, J., and Patterson, R.: Production of Antibody in the Canine Tracheal Pouch After Local and Systemic Influenza Immunization. J. Immun. (in press).

16. Patterson, R., Fink, J.N., Pruzansky, J.J, Reed, C., Roberts, M., Slavin, R., and Zeiss, C.R.: Serum Immunoglobulin Levels in Pulmonary Allergic Aspergillosis with Special Reference to IgE. Am. J. Med. (in press).

17. Fink, J.N., Hensley, G.T., and Barboriak, J.J.: An Animal Model of Hypersensitivity Pneumonitis. J. Allerg. 46: 156-161, 1970.

18. Zaidi, S.H., Dogra, R.K.S., Shanker, R., and Chavdra, S.V.: Experimental Farmer's Lung In Guinea Pigs. J. Path. 105: 41-48, 1971.

19. Seal, R.M.E., Hapke, E.J., Thomas, G.O., Meek, J.C., and Hayes, M.: The Pathology of the Acute and Chronic Stages of Farmer's Lung. Thorax. 23: 469-489, 1968.

20. Banaszak, E.F., Thiede, W.H., Fink, J.N.: Hypersensitivity Pneumonitis Due to Contamination of an Air Conditioner. New Eng. J. Med. 283: 271-276, 1970.

21. Sweet, L.C., Anderson, J.A., Callies, Q.C., and Coates, E.O., Jr.: Hypersensitivity Pneumonitis Related to a Home Furnace Humidifier. J. Allerg. Clin. Immun. 48: 171-178, 1971.

22. Kawai, T., Arquenbourg, P., Salvaggio, J., and Marsh, D.: Detection of Anti-House Dust Precipitins in Man. J. Allerg. Clin. Immun. 49: 134-135, 1972.

PANEL VII

GRANULOMATOUS LUNG DISEASES

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GRANULOMATOUS LUNG DISEASES

INTRODUCTION

Granulomatous diseases of the lung include sarcoidosis, Wegener's granulomatosis and eosinophilic granuloma. These disorders represent a borderland between infections and neoplasms. Sarcoidosis has histologic features resembling those of mycobacterial and fungal infections, while the response to cytotoxic drugs of Wegener's granulomatosis and eosinophilic granuloma resembles that of neoplasms. The three diseases have pathologic resemblances but differ in epidemiologic and immunologic characteristics. The cause and pathogenesis of this group of diseases remain unknown.

Sarcoidosis has been widely investigated, employing microbiologic, toxicologic, and immunologic methods, without success in determining etiology or in producing a model in experimental animals which resembles the disease seen in man. These investigations, however, have revealed that sarcoidosis is a disease with extraordinary immunologic characteristics: most patients have a permanent disturbance of delayed hypersensitivity responses, a moderate and seemingly nonspecific increase in certain circulating antibodies, and transient or prolonged reactivity to Kveim antigens.

Similar changes have not been demonstrated in Wegener's granulomatosis and eosinophilic granuloma, but the pathologic features of these disorders suggest that immunologic processes are also involved in these diseases.

MAGNITUDE OF THE PROBLEM

Of the diseases addressed by the panel, only sarcoidosis is prevalent enough to be considered a national health problem. However, all three disorders have considerable economic consequences because they occur in early and middle adult life. Sarcoidosis usually appears between ages 20 and 35, is more common in women, and is 12 to 15 times more common among Blacks. Radiologic surveys have indicated a prevalence as high as 40 per hundred thousand in black women. The frequency of sarcoidosis is even higher in women of the same age in Sweden (1). Accurate data on the annual incidence of sarcoidosis are available only from Great Britain and Denmark, where rates of approximately 5 new cases per 100,000 per year have been observed (2,3).

Sarcoidosis may affect distant parts of the body, but serious damage is most commonly pulmonary; it appears to play a greater role than has been appreciated in the genesis of pulmonary cysts and fibrosis and is not infrequently responsible for severe disability. The disease varies remarkably in duration and severity. At one extreme it causes no symptoms, is detected only by chest Xray surveys and lasts only a few months, so that the number of persons affected may considerably exceed the number recognized. Since mild and transient

attacks of the disease permanently affect certain immunologic defense reactions, the numerous unrecognized cases may be not inconsequential. Several American studies indicate that a third of clinically recognized cases require treatment with corticosteroids, and, among these, disability and death are not uncommon.

Sarcoidosis now outranks tuberculosis, particularly among Blacks, as a cause of disability due to pulmonary insufficiency and blindness. In 10 to 20 per cent of patients with sarcoidosis, severe disability occurs because of cardiorespiratory failure, damage to other organs, and superimposed infections.

Mortality data are not reliable since in the past deaths from sarcoidosis were often attributed, in error, to tuberculosis. An analysis of 35 deaths that occurred among patients under observation in Philadelphia reveals that 10 were under the age of 35 at the time of death; the mean age was 43 years. Deaths in this sample were disproportionately frequent among Blacks, but Veterans Administration data indicate that black and white men with sarcoidosis have similar mortality rates (4).

Progression may occur despite early diagnosis and prompt administration of corticosteroid therapy, so that greater availability of skilled medical care with consequent earlier recognition will only partially reduce morbidity and mortality from sarcoidosis.

The other granulomatous disorders are less common. The pulmonary form of eosinophilic granuloma exhibits an even more restricted age prevalence than sarcoidosis, and is recognized most often in young men in military service. Wegener's granulomatosis represents a disorder which until recently appeared to be almost invariably fatal; no ethnic, sex or age pattern of occurrence has been observed in this disease.

In many pulmonary diseases it is only necessary to persuade the public to put into practice currently available methods of prevention. Until research elucidates the cause or nature of sarcoidosis, no reduction in morbidity is likely.

CURRENT STATE OF KNOWLEDGE

Etiology

Epidemiologic studies have demonstrated an uneven distribution of sarcoidosis, with greatest frequency in Northern Europe, the United States, and Australia, and least in underdeveloped countries. It is uncertain whether environmental or geographic factors or variations in diagnostic resources are responsible for the difference in world-wide distribution of sarcoidosis. A recent Veterans Administration study suggests that ethnic factors are more important than environmental ones (4).

It is a remarkable fact that sarcoidosis is most prevalent in North Europeans and black Americans. Detection of a genetic or environmental factor common to these seemingly disparate populations should provide an important clue to the cause of the disease.

It would be of interest to determine the host characteristics of subjects prior to the onset of manifest sarcoidosis, and also the frequency, in patients and controls, of allergic disorders, viral infections, bacterial infections, fungal infections, neoplasia and autoimmune diseases. Such studies should include measurements of antibody responses to immunization, delayed hypersensitivity tests, storage of frozen sera, etc. Several population groups should be considered for such studies: offspring and younger siblings of patients with sarcoidosis, student nurses and medical students, since these groups have a higher likelihood of recognition of sarcoidosis; comparable ethnic groups in rural South and urban North, to determine possible effects of air pollution and other geographic differences. There should be further study of genetic mechanisms in the familial occurrence of sarcoidosis, and an attempt made to determine whether the concentration of sarcoidosis in the 3rd and 4th decades is a reflection of constitutional factors or of exposure to infectious agents.

Microbiologic investigations have revealed little evidence that sarcoidosis is an infectious disease. Nevertheless, belief in a relationship to mycobacterial infection persists for several reasons. The original concern was largely based on the frequency with which patients with sarcoidosis developed tuberculosis, but this association has disappeared in advanced countries as tuberculosis has declined. Tuberculosis is no longer a common complication of sarcoidosis, and the failure of sarcoidosis to decline suggests that tubercle bacilli are not an etiologic factor. Although efforts to culture mycobacteria regularly in sarcoidosis have been unsuccessful, reports continue to appear regarding the occurrence of acid-fast rods in tissue sections. Recent electron microscopic studies, however, indicate that these structures are not mycobacteria (5).

Efforts at demonstration of fungi and viruses, either at the onset of sarcoidosis or as a complication, have revealed no consistent relationship other than an increased susceptibility of patients with sarcoidosis to infection with cryptococcus and aspergillus. Recent studies (6) have failed to confirm reports that mycobacteriophages play a role in the genesis of sarcoidosis.

It appears safe to conclude that microbiologic studies have excluded infectious agents, with the exception of slow viruses and host-dependent bacteria. Further study of a possible etiologic role of these types of infection is indicated.

Pathogenesis

The altered *immunologic characteristics* demonstrated in sarcoidosis resemble in certain respects those in a variety of other illnesses: Hodgkin's disease, inflammatory gut disease, primary biliary cirrhosis, leprosy, disseminated lupus and chronic lymphadenitis of diverse causes. None of these, however, manifests so consistently the pattern of granulomatous responses to intracutaneous injection of Kveim test suspension, persistent impairment of delayed hypersensitivity, and an increase in circulating antibody responses to some viral antigens.

The mechanism of the impaired delayed hypersensitivity responses of patients with sarcoidosis has been extensively studied. In recent years the anergy has been regarded as due to abnormality of the T-lymphocyte system, but it has been observed (7) that despite cutaneous anergy, the lymphocytes of sarcoidosis patients were sensitive to antigens in vitro. These workers postulate that circulating blocking antibodies are increased in sarcoidosis.

An important characteristic of the anergy is that it persists for years after transient episodes of sarcoidosis. Inability to remember sensitivity, rather than inability to develop it, appears to be the cardinal feature of sarcoidosis after immunization with BCG, injection of transfer factor or following tuberculosis. Tuberculin sensitivity develops but quickly wanes. Confirmation of the sensitivity of lymphocytes of patients with sarcoidosis to antigens in vitro would alter the direction of immunologic study of sarcoidosis to a greater emphasis on humoral factors, and further study of the serum immunoglobulins, which have thus far shown inconstant variations from normal.

Studies of transfer of cellular hypersensitivity are of special interest because of a recent observation (8) by an investigator who gave transfer factor from leucocytes of tuberculoid leprosy cases to patients with lepromatous leprosy. Although no long-term therapeutic improvement was obtained, it was noted that 4 of 9 patients developed erythema nodosum or arthralgia shortly after transfer. The relationship of erythema nodosum and sarcoidosis is a fascinating one. The two are commonly associated in North Europeans, less often in Puerto Ricans and infrequently in Americans born on the mainland. The course of sarcoidosis is usually more benign in patients who have erythema nodosum. An explanation of the genesis of erythema nodosum in immunologic terms should contribute greatly to our understanding of sarcoidosis.

Ethical objection to transfer of cells from one patient to another should be minimized if both patients have the same disease. It would be most informative to ascertain whether administration of transfer factor from Kveim-positive patients to Kveim-negative patients with sarcoidosis will induce reactivity. Conversely, if transfer factor from Kveim-negative cases abolished the reaction of Kveim-positive cases, therapeutic benefits might be obtained.

The list of immunologic investigations applicable in sarcoidosis is long; extension of blast transformation studies, T and B cell counts and measurement of their life span in granulomatous lungs; study of the various lumphokines; examination of sarcoid sera for immunosuppressive factors; analysis of the HL-A histocompatibility system. Proficiency in all of these approaches cannot be anticipated in a single institution. It would appear more profitable for a center focused on clinical and immunologic study of sarcoidosis to serve as a bank or clearing house, providing cells, sera and tissues to investigators developing the techniques enumerated above. In every field of immunologic research, the availability of specimens from carefully studied and classified patients with sarcoidosis should be of great value.

Since improved in vitro techniques for measurements of lymphocyte responses are essential to make rapid and precise diagnosis of sarcoidosis possible when standardized antigens are available, investigation in this field should be intensified.

Study is indicated in an effort to determine late consequences of the immunologic abnormalities present in sarcoidosis, such as an increased susceptibility to Hodgkin's disease.

Clinical Aspects

Although *diagnosis* is accomplished with a reasonable degree of accuracy in the majority of cases of sarcoidosis with presently available methods of tissue biopsy, an immunologic test for diagnosis should provide a significant reduction in hospitalization costs since a specific in vivo or in vitro test would permit diagnosis in out-patients.

Major attention has been given to the *Kveim reaction* because of its promise as a means of differentiating sarcoidosis from other diseases. Even more compelling has been the anticipation that isolation of the specific factor in Kveim test preparations would reveal the cause of sarcoidosis.

The problems of preparation, standardization and interpretation of Kveim tests have not been solved. No single suspension is widely available to investigators, and it has recently been shown that different lots of test material differ in their behavior.

The explanation may rest in slight differences in antigenic constitution, in minor alterations in methods of preparation, or to unexplained deterioration of the test materials. Differences in histologic interpretation may be in part responsible for conflicting results with the test. The possibility of a genetic factor in responses to the Kveim test is suggested by the observation of an increased frequency of positive reactions in Orientals with leprosy (9,10).

Uncertainty regarding the diagnostic specificity of the Kveim reaction has interrupted promising progress toward development of in vitro methods of diagnosis of sarcoidosis. One recent study has employed migration inhibition factor measurements as an indication of sensitivity of lymphocytes,cultured from sarcoidosis patients, to Kveim antigen (7). An obstacle to identification of a specific antigen in Kveim test materials has been the finding that the active agent is particulate: activity appears to reside within the subcellular particles of the test suspensions (11). It has been suggested that cytoplasmic particles represent exogenous material phagocytized by epitheloid cells, but an endogenous or tissue origin has not been excluded. Treatments which ordinarily denature protein, remove lipids or inactivate carbohydrate moieties do not destroy the activity of Kveim suspensions.

The diagnostic use of the Kveim test has in the past been impeded by numerous obstacles. The interval of 6 weeks required for completion of the test and the need for withholding cortiocosteroid therapy during this interval has limited the applicability of this test in ill and hospitalized patients. Concern about transmission of hepatitis has been a factor in delaying federal approval of its distribution. These problems should be obviated by the development of in vitro methods of demonstrating sensitivity to Kveim antigen of lymphocytes of patients with sarcoidosis.

The development of a reliable and specific in vitro test for sarcoidosis would represent a major clinical advance of importance not only to the many patients who have sarcoidosis, but to physicians and surgeons in virtually every speciality for whom sarcoidosis is a frequent diagnostic consideration. It is likely also to represent an immunologic breakthrough which would advance the understanding of many other illnesses as well as of normal defense mechanisms. A prime need is for a Kveim test antigen which does not react in patients with inflammatory gut disease, disseminated lupus and adenopathies of diverse etiology and which can be generally distributed for investigative and diagnostic purposes with monitoring to ensure that potency and specificity of test materials are maintained. Commercial production would undoubtedly soon be undertaken because of the wide demand for Kveim test materials.

Kveim test preparations used in the past have been prepared from lymph nodes and spleens. Since tissue antigens may be responsible for the granulomatous response, an important step would be the preparation and testing of extracts of other tissues, such as sarcoid lung or liver, as well as spleens and lymph nodes diffusely involved by granulomas of other etiology.

Immunochemical procedures should be used to the fullest extent possible in an effort to establish the source and nature of the Kveim test antigens. If environmental constituents were demonstrated, it

would provide an important clue to the etiology of sarcoidosis. Failure to demonstrate exogenous factors would strengthen the concept that sarcoidosis is an immunologic over-reaction to trivial or miscellaneous environmental insults. Increased reactants to histocompatibility antigens have been recognized in patients with lymphomatous, leukemic and collagen diseases, and investigation is indicated to determine whether HLA antigens may be involved in the Kveim reaction.

Further identification of the nature of the antigen should be pursued by immunofluorescence studies, as these may provide evidence as to whether these factors are of tissue or of environmental origin.

Extensive investigation has been carried out on the *physiologic disturbances* resulting from pulmonary infiltration by sarcoidosis. The nature and degree of ventilatory and respiratory insufficiency appear related to the amount of granulomatous inflammation or fibrosis which is present. The most promising physiologic approaches at present would be those involving study of the metabolic and defense functions of the lung.

There is general agreement regarding indications for presently available *methods of treatment*. Patients without symptoms, whose disease is confined to the mediastinal and hilar lymph nodes, are not treated, while cortiocosteroid therapy is useful in suppressing inflammatory changes in patients ill with fever, respiratory, musculoskeletal, myocardial, central nervous system or other systemic manifestations of the disease. The only area of disagreement is a relatively small one concerning the value of cortiocosteroid therapy in patients whose symptoms are minimal but who have persistent or increasing pulmonary infiltrations. Although controlled clinical trials using corticosteroids for short periods indicate that the use of corticosteroids does not alter the eventual outcome, a few investigators advocate the prolonged use of corticosteroids. Treatment of this prolonged character cannot be assessed by double-blind trials and its value in averting fibrosis must remain speculative. The superiority of cytotoxic or immunosuppressive drugs in Wegener's granulomatosis and eosiniophilic granuloma over corticosteroids suggests the advisability of further trials of these agents in sarcoidosis. Preliminary reports of benefit from their use in sarcoidosis appear to justify randomized trials comparing corticosteroid and cytotoxic drug therapy in patients with severe forms of this disease.

It appears that prevention and more satisfactory methods of treatment must await discovery of the etiology and pathogenesis of the disease. Although a great mass of observations have been accumulated regarding the clinical features of the granulomatous diseases, there is need for interpreting these data in immunologic, pathologic and physiologic terms.

Models

Efforts to produce a satisfactory model of sarcoidosis in experimental animals have been unsuccessful. However, several investigators have succeeded in producing local granulomas resembling the epithelioid tubercle of sarcoidosis at the sites of injection of pine pollen extracts and other irritants. Disseminated granulomatosis was obtained in one strain of guinea pigs by injection of Freund's adjuvant, and similar injections have produced transient pulmonary granulomas in other animals. Recently disseminated chronic granulomatosis has been induced by two groups of workers who injected sarcoid lymph node homogenates into the foot pads of mice (12,13). This evidence of a transmissible factor represents a major advance that deserves intensive investigation. Another promising new approach is suggested by the report of production of pulmonary granulomatosis produced by intravenous injection of bentonite particles coated with soluble antigens from schistosome eggs as well as with antigens derived from a filtrate of mycobacterium tuberculosis (14).

Macrophage nodulization at sites of antigen deposition to form granulomas is immunologically directed by sensitized lymphocytes. Bronchopulmonary lavage should be employed in an effort to obtain specifically reactive lymphocytes which may be more numerous in diseased tissues than in the blood stream, and more numerous in the lung since reactive cells may be trapped in the pulmonary capillaries.

It would be useful to expose primates to a variety of inhalation exposures in an effort to produce granulomas with an anatomic distribution and behavior consistent with sarcoidosis. This would provide an opportunity also for ascertaining whether the immunologic alterations characteristic of sarcoidosis are essential to the formation or dissemination of the granulomas.

Cell culture of sarcoid tissues has been attempted with occasional success. Further attention should be given this approach in the hope of securing antigens or evidence of an infectious agent in cell lines derived from granulomas in various tissues. Enzyme biochemistry at the electron microscopic level may identify the function and activity of these cells.

CONCLUSIONS

I

Much of the early research in sarcoidosis was epidemiologic and bacteriologic, inspired by the belief that this disease was an atypical form of tuberculosis, and that geographic factors were the determining influences in the etiology of the disaese. Thorough studies have in part dispelled both of these hypotheses, and at present the most promising avenues toward solution of the cause of sarcoidosis appear to rest in its immunological characteristics.

Because of its promise as a means of differentiating sarcoidosis from other diseases, the Kveim reaction has received major attention. But the problems of preparation, standardization, and interpretation of these tests have not been solved. Corticosteroid therapy must be withheld during the weeks required for completion of the Kveim test, a major drawback in seriously ill patients.

Development of a reliable, specific in vitro test for sarcoidosis would represent a major clinical advance, of importance not only to patients, but also to physicians and surgeons for whom sarcoidosis is a frequent diagnostic consideration. It would also represent an immunologic breakthrough that would advance the understanding of many other illnesses as well as normal defense mechanisms.

II

Development of methods of diagnosing, preventing or treating sarcoidosis can only be achieved through a multidisciplinary approach in which immunology, pathology and physiology contribute to studies of patients with the disease.

Knowledge necessary for an understanding of the etiology, pathogenesis and pathophysiology of sarcoidosis can best be attained in a multidisciplinary center where large numbers of patients are available and experts in relevant disciplines work in close cooperation with clinicians.

RECOMMENDATIONS

MULTIDISCIPLINARY CENTERS HAVING ACCESS TO LARGE NUMBERS OF PATIENTS SHOULD BE DEVELOPED FOR STUDY OF SARCOIDOSIS. SUCH CENTERS SHOULD USE IMMUNOCHEMICAL, IMMUNOLOGIC, AND CLINICAL APPROACHES TO STUDY THE PATHOGENESIS OF THE DISEASE AND TO DEVELOP AN IN VITRO TEST FOR ITS DIAGNOSIS.

APPROACHES SHOULD INCLUDE PREPARATION AND IN VIVO AND IN VITRO TESTS OF ANTIGENS FROM VARIOUS GRANULOMATOUS TISSUES AND SPLENIC EXTRACTS, STUDIES OF TRANSFER FACTOR IN PATIENTS WITH SARCOIDOSIS, AND THE DEVELOPMENT OF IN VITRO METHODS OF MEASURING LYMPHOCYTE SENSITIZATION TO ANTIGENS.

THESE CENTERS SHOULD ALSO PROVIDE OTHER INVESTIGATORS WITH TISSUES, CELLS AND SERA FROM CAREFULLY STUDIED AND CLASSIFIED CASES OF PULMONARY GRANULOMATOSIS.

REFERENCES

1. Lofgren, S.: Diagnosis and Incidence of Sarcoidosis. Brit. J. Tuber. 51: 8-13, 1957.

2. British Thoracic and Tuberculosis Assn. Geographical Variations in the Incidence of Sarcoidosis in Great Britain: A Comparative Study of Four Areas. Tubercle. 50: 211-231, 1969.

3. Horwitz, O., Payne, P.G., and Wilbek, E.: Epidemiology of Sarcoidosis in Denmark. Danish Med. Bul. 14: 178-182, 1967.

4. Keller, A.Z.: Hospital, Age, Racial, Occupational, Geographical, Clinical and Survivorship Characteristics in the Epidemiology of Sarcoidosis. Am. J. Epid. 94: 222-230, 1971.

5. Leake, E.S. and Myrvik, Q. N.: Osmiophilic Structures in Granulomatous Macrophages and the Problem of Intracellular Mycobacteria. Am. Rev. Resp. Dis. 104: 132-133, 1971.

6. Bowman, B.U., Amos, W.T. and Geer, J.C.: Failure to Produce Experimental Sarcoidosis in Guinea Pigs with Mycobacterium tuberculosis and Mycobacteriophage D S6A. Am. Rev. Resp. Dis. 105: 85-94, 1972.

7. Caspary, E.A. and Field, E. J.: Lymphocyte Sensitization in Sarcoidosis. Brit. Med. J. 2: 143-145, 1971.

8. Bullock, W.E., Fields, J. and Brandriss, M.: Transfer Factor Therapy in Lepromatous Leprosy: An Evaluation. J. Clin. Invest. 50: 16a (Abstract 51), 1971.

9. Rees, R.J.W.: The Kveim Test in Leprosy. Postgrad. Med. J. 46: 486-490, 1970.

10. Bovornkitti, S.: Kveim Tests in Leprosy. Presented at 6th International Conference on Sarcoidosis, Tokyo, September 1972.

11. Siltzbach, L.E. and Ruttenberg, M.A.: Chemical and Physical Characteristics of the Active Principle in Kveim Suspensions. Proc. 5th Intern. Conf. Sarcoid. Univ. Karlova Press, Prague, pp. 371-374, 1971.

12. Mitchell, D.N. and Rees, R.J.W.: The Production of Granulomas in Mice by Sarcoid Tissue Suspensions. Presented at 6th International Conf. on Sarcoidosis, Tokyo, September, 1972.

13. Taub, R.N. and Siltzbach, L.E.: Induction of Granulomas in Mice by Injection of Human Sarcoid and Ileitis Hemogenates. Presented at 6th International Conf. on Sarcoidosis, Tokyo, September, 1972.

14. Boros, D.L. and Warren, K.S.: Specific Granulomatous Hypersensitivity Elicited by Bentonite Particles Coated with Soluble Antigens From Schistosome Eggs and Tubercle Bacilli. Nature 229: 200-201, 1971.

PANEL VIII

INFECTIOUS PNEUMONITIS

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INFECTIOUS PNEUMONITIS

INTRODUCTION

The panel addressed itself to all diseases of the tracheo-bronchial tree and of the lungs that are caused by infectious agents. It was mostly concerned with clearly identifiable infectious diseases that occur either as self-limited episodes or as chronic diseases leading to lung destruction. The panel did not consider in depth those diseases in which infectious agents might act as antigens that produce reaginic mediated lung disease (e.g., asthma), or diseases in which infectious agents act on proteins to produce antigens that are responsible for hypersensitivity pneumonitis. Moreover, although infectious agents may well be implicated as causes of chronic airways disease, emphysema, and non-specific pulmonary fibrosis, the panel did not address itself specifically to these diseases.

MAGNITUDE OF THE PROBLEM

Infectious pneumonitis constitutes one of the most frequent health problems in this country and is the single most common cause of hospitalization due to respiratory disease. Data on short-term hospitalization from the Hospital Record Survey of the Commission on Professional Hospital Activities reveal that infectious pneumonitis from all causes was responsible for about 2.7 million hospitalizations in 1970, or 8.5 percent of the 33 million hospital discharges surveyed in that year (1).

In addition, infectious pneumonitis contributes significantly to the overall problem of nosocomial (hospital acquired) infections. Approximately one percent of all patients admitted to short-term hospitals throughout the country develop a nosocomial infectious pneumonitis. Many of these cases are caused by gram negative organisms. Nosocomial infectious pneumonitis has been estimated to delay discharge from the hospital by approximately seven days. Thus, estimating 329,000 patients who develop infectious pneumonitis while hospitalized, more than 2.3 million hospital-days are added to those for the basic illness.

Mortality data from the National Center for Health Statistics show that in 1968 there were 193,000 deaths in this country due to all diseases of the respiratory tract (2). Of these, 34 percent were due to infectious pneumonitis, making pneumonia one of the most common causes of respiratory mortality, accounting for 34.9 deaths per 100,000 persons. For children less than one year old, approximately 12 percent of all deaths were due to respiratory diseases; pneumonia also accounted for the majority of these.

Respiratory infections are frequently a cause of "excess mortality", a term used to indicate deaths that occur beyond the number predicted for a given period of time. Mortality data available from the National Center for Health Statistics and analyzed at the National Center for Disease Control reveal that there were approximately 275,000 "excess" deaths between 1957 and 1972 as a consequence of influenza infections (3).

The socioeconomic impact of infectious diseases of the respiratory tract is very difficult to assess. On the basis of data available for 1967, the total cost of infectious pneumonitis has been estimated to be $2.067 billion for that year. The panel believes this to be a very conservative estimate of the problem at the present time given the problems of the reporting system and the lack of complete updated statistics. However, mortality and hospitalization data alone highlight the problem of infectious pneumonitis as one of the key problems in respiratory disease.

CURRENT STATE OF KNOWLEDGE

Etiologic Factors

Organisms capable of primary infection of the lung include bacteria, viruses, mycoplasma, mycobacteria and some fungi. Most bacterial and mycotic infections become established after host defenses are impaired. In relatively resistant hosts, the influenza virus is eradicated rapidly from the body. Primary mycobacterial infections are controlled by cellular immune hypersensitivity reactions. However, where host defenses are impaired, virus infection may progress rapidly to death. The failure of cellular and humoral immunologic responses permit mycobacterial infection to continue, multiply, spread by local invasion, or disseminate to distant points. Some specific etiologic agents of importance to national health are discussed below.

Mycoplasma pneumoniae develops in 3 to 10 percent of infected persons (4). Although infection is known to occur in epidemics among military populations and in household outbreaks, its epidemiology and true prevalence remain to be elucidated. M. *pneumoniae* are susceptible to tetracycline and erythromycin, and treatment with these agents may shorten the course of illness, but the organisms may persist in the pharynx. The role of antibiotic therapy in modifying the spread of infection is unknown, and circumstances analogous to the "immune carrier" may exist.

Diplococcus pneumoniae remains responsible for approximately 80 percent of bacterial pneumonias. The incidence of pneumococcal disease is estimated at one case per thousand persons per year (5). Of these, an estimated one-quarter to one-third are associated with bacteremia. In patients with bacteremic pneumonia the mortality rate varies with age: individuals less than 50 years of age, 9 percent; those 50 years or older, 30 percent (6). It has been shown that administration of Types I, II and III pneumococcal polysaccharide to persons over 50 years of age was associated with a 90 percent decrease in infection due to to these types (7). Recent studies have shown that pneumococcal Types I, III, IV, VII, VIII and XII account for 55 to 60 percent of pneumococcal bacteremias in adults (5). Based upon such data it is estimated that 20,000 deaths per year could be prevented if a vaccine of this efficacy were administered to all older adults. An additional consideration is the observation that strains of D. *pneumoniae* with increased degrees of resistance to penicillin G have been isolated in New Guinea, and a strain which is highly resistant to tetracycline and erythromycin is isolated from 1 to 10 percent of patients in the United States (8).

With the decline in *Bordetella pertussis* which followed the use of standardized pertussis vaccine, there remain a number of poorly defined but potentially important problems. The level of protective immunity achieved by the administration of DPT vaccine in childhood lapses by the time an individual is in his teens (9). Pertussis which is not associated with classical "whooping" is now recognized as occurring in young adults with tracheobronchitis (10). Such adult type pertussis may be of more than nuisance concern. The importance of childhood whooping cough in the genesis of pulmonary disease has been recognized, and it seems reasonable to assume that adult type pertussis also might be of significance.

Mycobacterium tuberculosis continues to be an important problem among certain population groups in the United States, especially those of low socioeconomic background. The current approach toward tuberculosis control in the United States, i. e., detection of infection (tuberculin testing) and chemoprophylaxis, has encountered a series of recently recognized difficulties.

Major causes of nosocomial pneumonia are gram negative bacilli, staphylococci and other opportunistic agents which colonize seriously ill patients. The panel believes that this serious problem will best be controlled by a better understanding of host defense mechanisms and careful epidemiologic studies of hospital acquired pneumonia.

Pneumocystis carinii infections are being recognized with increasing frequency in patients receiving immunosuppressive agents and steroids after renal transplantation. There is currently no reasonably accurate noninvasive technique for the diagnosis of such infections. Inasmuch as a therapeutic agent is available, there is a need for rapid diagnostic procedures.

Associated etiological factors include environmental toxic agents such as pollutant gases and particles, including occupational dust exposures. For example, there is a well-defined relationship between silicosis and susceptibility to tuberculosis that illustrates the relationship between environmental toxic agents, host defense mechanisms and specific invaders. Occupational group exposures to mineral (silica, asbestos and coal) and organic dusts (cotton and diisocyanates), gases (NO_2 and SO_2), fumes, and hydrocarbons are important co-factors for a few infectious pulmonary diseases. Low socioeconomic position with all it implies clearly needs study as a complex co-factor including crowded quarters, poor heating or cooling, accumulation of garbage and resultant pests and even different patterns of cigarette smoking.

Host Defense Mechanisms

Host defenses have a major role in preventing the establishment of infections or in limiting the multiplication and spread of microorganisms that cause infectious pneumonitis. Defense mechanisms may be affected by a variety of endogenous factors (genetic, immunologic, structural, endocrinologic, metabolic, or chronic disease) as well as by exposure to exogenous agents such as pollutant gases and particles.

Transport pathways and mechanisms for processing particles which reach the lung (11) contribute to host defenses. Mucus transport in the bronchi depends on the integrity of ciliated epithelial cells and on the quantity and constituents of mucus, including immunoglobulin A, lysozyme, interferon and other materials. The mucus transport system has been extensively studied, and it has been demonstrated that many toxic agents (NH_3, NO_2, acrolein, formaldehyde, cyanide, etc.) interfere with ciliary action, and that these and other agents also stimulate secretion of mucus. Destruction or alteration of this transport system delays clearance of deposited material and increases storage in the lung. Relatively little is known as to whether the mucociliary transport apparatus helps to remove particles from alveoli, and almost nothing is known about how viruses affect mucociliary transport.

Studies of mucociliary transport in vivo and in vitro are based on the hypothesis that delayed mucociliary transport, due to inhibition of ciliary movement or abnormal mucus secretions, leads to increased susceptibility to bacterial infections. Studies in humans have shown that mucociliary transport is surprisingly variable in normal subjects (12) and in those with chronic bronchitis (13). Delayed transport associated with thick mucus secretions in proximal airways may be corrected by coughing. Further study to determine whether impairment of mucociliary transport of microbial agents leads to infections in the lung is necessary.

Methods are available to collect sufficient quantities of tracheal mucus via tracheal pouches, esophageal cannulae, etc., to characterize the properties of mucus in healthy animals and those with induced disease, and to compare with data on ovine and bovine cervical mucus. Simple in vitro experiments could elucidate the effect of pH, divalent cations, urea, proteolytic agents, oxidants, metallic ions, drugs, bacteria and viruses on tracheal mucus. Likewise, the content of secretory immunoglobin A, lysozyme, interferon and other materials could be determined. Studies should be extended in vitro to evaluate changes in permeability, hydration, ion concentration and pH on defense functions.

The generation and flow of lymph from the distal alveolar ducts, the precise role of lymphatic pathways in normal clearance, and their role as an augmenting transport pathway during inflammation, are unknown. These primary and secondary transport pathways are particularly important in infectious pneumonitis, since the establishment of inflammation in the lung leads to the recruitment of additional transport pathways to deal with multiplication and spread of infectious agents. Tissue resistance to infection depends not only on the integrity of the bronchial tree but also on the integrity of the pulmonary lobule and its lymphatic system, which drains both centripetally to the bronchiolar system and centrifugally to the perilobular veins. The contribution of the several transport pathways and their involvement in different diseases requires further investigation.

The alveolar macrophage system is another important component of host defense systems (14). This system depends primarily on the metabolic and enzymatic apparatus of the alveolar macrophages and their many intracellular factors, which function to contain or eradicate microorganisms (15). These intracellular factors include the properties of lysosomal enzymes and the microbicidal substances (such as hydrogen peroxide), which are elaborated in the metabolic burst accompanying the phagocytic process (16). The alveolar macrophages can be augmented by the recruitable phagocytic systems of bone marrow; namely, polymorphonuclear leukocytes, monocytes, macrophages and histiocytes.

Particle uptake is influenced by the presence of opsonins, specific antibodies, cellular immune factors, etc., which, in turn, depend on local and systemic production of the several classes of immunoglobulins plus immune lymphocytes. Effective uptake and intracellular processing of infective and chemical particles also involve the complement system and other chemical mediators, cellular factors, leukotactic factor, migration inhibition factor, etc, as well as other substances elaborated in the phagocytic and inflammatory process to help localize and control infectious pneumonitis. In the process of inflammation, various proteolytic enzymes are released from cells and must be controlled by antiproteolytic enzymes. The potential for defective function in the uptake and intracellular processing of particles during phagocytosis is multiple. They include not only alterations in the phagocytic cell, but also factors that involve the local and systemic immunologic apparatus. This complex of mechanisms, that ends with phagocytosis as a final common pathway, has received a great deal of study in vitro but relatively little in the lung.

Phagocytic mechanisms in the lung have received renewed attention in connection with pulmonary infections. Extensive studies of phagocytosis using peripheral blood leukocytes and peritoneal histiocytes performed in the past two decades have elucidated many of the cellular mechanisms and metabolic activities involved in the host's handling of foreign materials. Recently, increasing attention has been paid to the alveolar macrophage as the prominent phagocytic mechanism in the lung. These studies have been based largely on cells obtained by washout techniques and relatively few studies have been performed on the phagocytic system in vivo. Although in vitro studies are important in certain aspects of studies of phagocytic physiology, methods are now available to assess phagocytosis in vivo (17). Since in vivo and in vitro phagocytic conditions vary considerably, efforts should be directed at developing methods for in vivo measurement of phagocytosis for comparison with the studies on lung washout cells. This technique has been directed principally toward animal studies but now receives increasing application in human studies. Extensive studies of intracellular phenomena involving phagosomes, lysosomes, membrane enzymes, etc., are important to the understanding of phagocytic mechanisms and probably can be obtained only by in vitro study. Tissue culture methodology is a powerful tool to insert between studies of freshly washed out lung cells and the intact lung. It permits changes in environmental or metabolic conditions singly without the host's compensatory responses. Research should relate these in vitro studies directly to in vivo findings and to hypotheses concerning disease mechanisms. These techniques should be applied to problems and not used merely as a data-oriented methodology.

Surfactant, which has been extensively studied as a physical layer on alveolar walls, that promotes alveolar stability, should be investigated as an alveolar defense mechanism. It should be studied in vitro for its effects on bacteria and viruses in relation to phagocytosis of these cells. It should also be investigated in vivo to determine whether specific metabolic changes (such as addition of cholesterol, fatty acids or hydrocarbons) alter its defensive capacity (18).

Pathogenesis

Infectious pneumonitis occurs because of breakdown of a complex of systems involving tissue architecture, transport mechanisms, phagocytic mechanisms, antibodies, cellular immune factors, and metabolic responses. Endogenous disease or environmental toxic agents can interrupt these systems at specific points enabling multiplication of microorganisms with resultant invasive pneumonia, chronic interstitial infection, systemic infection or perhaps bacterial multiplication limited to the mucus layer within airway lumens. Moreover, although pulmonary infection results from breakdown of host defense mechanisms, an established infection may itself further compromise host defenses and lead to its own perpetuation (for example, bronchiectasis), or to a secondary infection with a different infectious agent (for example, staphylococcal pneumonia following influenza).

Surface coverings (surfactant and mucus), the phagocytic, and the transport systems may potentially be damaged by inhaled environmental agents, particularly toxic gases. Thus, cigarette smoke and air pollutants suppress particle uptake and influence intracellular processing and the lymphocyte immune apparatus (19). In the pathogenesis of infectious pneumonitis, exposure to environmental substances which are toxic to phagocytes, or the administration of immunosuppressive agents, is of primary concern because of reduction or loss of these host defenses. Resistance is further influenced by the presence of chronic disease in the lung or in other organs which may add metabolic abnormalities such as acidosis to the defense suppressing activity of environmental agents (23). Specific immunity to one or another of the challenging microorganisms has a significant effect on the magnitude of impairment produced by environmental toxic agents or host disease processes (12).

Some infections, such as pneumococcal pneumonia, are characterized by a remarkable orderly sequence of events: pulmonary edema (perhaps supplying water and immunoproteins and other materials); containment within lung segments or lobes; cellular recruitment, first of polymorphonuclear leukocytes then of mononuclear macrophages; and, finally, orderly removal of reaction products from alveoli to restore structure and function to normal. Other infections, such as that by influenza virus, have a rampant pulmonary edema phase which may never progress to a cellular phase. Still others, such as tuberculosis, follow the pneumococcal pattern, but instead of removal of debris and resolution go onward to attempted storage of cell products, including proteolytic enzymes and indigestible matter, producing necrosis and sequestration by caseation and fibrosis.

The monitoring and regulation of the transitions between *stages of inflammation* appear to be host determined. On superficial analysis, inflammation may be regulated by the success of proteolysis and other digestive efforts plus the degree of removal of the denatured, lysed and otherwise altered proteins, cells and cell products from alveoli. Clearly

this cascade of response must be studied and the contribution of infective agents, environmental co-factors and the many components of the hosts defense system determined.

The relationship between *cellular immunity* in the lung and resistance to intracellular organisms has received, as yet, inadequate study. Changes in cellular hypersensitivity may occur on exposure to environmental agents and in response to acute and chronic diseases which do affect the lung primarily. The major questions are how do the known immune mechanisms control and modulate inflammation, and are there other mechanisms still unknown. Immunologic events have been studied principally by measurements of the circulatory classes of immunoglobulins and to a lesser extent the secretory immunoglobulins found in the serum and in bronchial washings. Recent efforts have been directed toward measurements of indices of cellular immunity in the lung, including measurements of lymphoblast transformation and macrophage inhibition factor in lung washings (20).

Changes in connective tissue following injury to the lung warrant intensive study. The integrity of the lung depends upon connective tissue, including collagen, elastin, reticulin, smooth muscle and the ground substance of interstitial space, which is rich in hyaluronic acid. Inflammatory responses - except those which lead to storage of indigestible or irremovable debris - cause disease because of atrophy (emphysema) or metaplasia (fibrosis) of connective tissue; those pneumonias which fail to resolve either digest the architectural framework of the lung, or stimulate fibrosis which may be focal or diffuse. Little is known about the mechanism controlling these responses or the stimuli which elicit them, although proteolytic enzymes for the former and silica in the latter have been studied.

Viral infection sometimes impairs and delays *peripheral lung clearance* (21). Furthermore these studies suggest that there are clearance compartments which may reflect different mechanisms of transport out of the peripheral lung. Chronic pulmonary diseases which damage the alveolar and bronchiolar levels of the lung may delay clearance and may lead to long-term storage of particles in the distal lung. This may permit colonization by infectious agents and ultimately infection and disease. Relatively little work in this area exists beyond some preliminary studies of radiotracer particulate clearance from the peripheral portions of the lung (22). Documentation as to whether clearance compartments exist in the peripheral lung and what mechanisms influence clearance rates and clearance compartments is a prime area for research. It should then be determined whether defects in defined phases of particulate clearance are correlated with specific forms of infectious pneumonitis and other chronic bronchopulmonary disorders.

The development of *models* could contribute to an understanding of many of these problems. The mammalian lung is not accessible for direct observation and manipulation. Furthermore, it is difficult to visualize because of the unique air-fluid interfaces. Better models and more knowledge

of their uses and limitations would enable better understanding of the various functions of the lung both in vitro and in vivo. Examples include the Langmuir trough as a monolayer (permeable membrane) for respiratory gases and water in which to study lipid protein interactions, ciliated epithelium exposed in the open trachea, macrophages in wet mounts, cell and organoid tissue culture and simpler lungs as that of the bullfrog and rodents. Cell model building or development should be encouraged and there should be further detailed evaluation of existing models. Efforts should be directed to developing models to test hypotheses about disease.

Therapy

Approaches to viral diseases, especially influenza, should include consideration of newer vaccines, e.g., subunit vaccines, live attenuated vaccines, assessment of nonspecific immunoprophylaxis, accelerated investigation of antiviral agents, programs for making such agents available, and improved methods of supporting patients with acute pulmonary insufficiency due to influenza.

In vaccine trials for pneumococci it is essential to ascertain whether the ecological vacuum created will be filled with other types of pneumococci and whether these have similar degrees of potential virulence. Observations with Group C meningococcal vaccines have shown this phenomenon, but the Group B and Y strains which replace the Group C have a lower ratio of infection to disease, hence the use of a "partial immunization" program appears justifiable.

While there is an ongoing controversy regarding the efficacy of BCG for tuberculosis, there is no question that alternative approaches to chemoprophylaxis including immunoprophylaxis should be considered. Areas of potential value include the use of purified immunogenic components and the use of substances such as "transfer factor". Investigation to determine the shortest possible chemotherapeutic regimen for tuberculosis should be carried out. Basic investigation to determine if a means can be found to cause all infecting tubercle bacilli to multiply at one time can be found; presently available chemotherapeutic agents are tuberculocidal, but only in the multiplying phase of the bacteria. If all could be stimulated to multiply simultaneously, the focus of infection could likely be eradicated more promptly.

There is a need to define the problem and to explore more effective approaches to the treatment of the progressive or disseminated forms of fungal disease. Such approaches should include mandatory reporting of fungal diseases and alternative chemotherapeutic agents, but consideration should include immunoprophylaxis with either vaccines or materials such as "transfer factor". More specific knowledge concerning the growth characteristics of fungi should be investigated to determine their interaction with the lung and with their environment.

Investigation of specific infectious pneumonitis and the treatment of individual patients with infectious pneumonitis is seriously hampered by lack of simple and accurate means of diagnosis. Investigation into means of specific diagnosis in individual patients is considered highly deserving of support.

CONCLUSIONS

I

Although significant advances against infectious diseases of the lung will be made by research directed at specific disease entities, the most productive results will not be obtained solely in this manner. Specific therapy may cure acute manifestations of illness, but in many instances this is only after permanent damage has occurred to the lung. Moreover, man must continue to live in an environment of microorganisms which will gain access to the lung. The most promising approach is through elucidation of the mechanisms by which the body defends itself against such invading microorganisms. Important host defense mechanisms that warrant investigation include the mucociliary transport system, the alveolar macrophage system, surfactant, and mucus.

Research is needed to elucidate how the lung defends itself against infectious microorganisms.

II

Many host factors appear to modify the usual effects of infectious agents. Such host factors include age, sex, race and genetic contribution. Specific metabolic diseases (such as diabetes mellitus or cystic fibrosis) as well as immunologic diseases (such as multiple myoloma) also accentuate the effects of infectious agents. The menstrual cycle, which affects cells and mucus in the airways, may change their defensive roles.

Well designed population studies are needed to provide clues to host factors involved in the development and cure of infectious pneumonitis.

III

Among environmental factors affecting alveolar disease, one of the most important is a burden of small particles, products of combustion, against which the alveolus has inadequate phylogenic defenses. Currently most studies of environmental factors are simple toxicity studies of single agents on one mechanism of host defense. But other factors are believed to be important. These include obesity, alcoholism, vitamin A deficiency, general malnutrition especially in childhood, and ingestion of therapeutic and toxic chemicals. Occupational exposures to mineral and organic dusts are important co-factors for a few infectious pulmonary diseases. Low socioeconomic position with all it implies also clearly needs study as a complex co-factor.

Studies are needed which integrate the effects of exposure to toxic agents with specific host defenses. Studies of environmental pulmonary disease should include measurements which assess resistance to microbial infection in the lung and which measure the effects of infectious diseases on apparently primary environmental disorders. Studies of infectious agents should relate them to the multiple other factors that impinge on the lung at the time of infection and the complex effects of the multiple agents on the evolution of disease and of chronic lung damage.

RECOMMENDATIONS

I

MAJOR EMPHASIS SHOULD BE PLACED ON STUDIES OF LUNG DEFENSE MECHANISMS, THE INTERACTION OF INFECTIOUS AGENTS AND THE LUNG, AND THE INTERACTION OF OTHER FACTORS THAT MODIFY HOST DEFENSES. INTERDISCIPLINARY STUDIES ADDRESSED TO THESE PROBLEMS SHOULD BE ENCOURAGED AND FOSTERED.

SUCH STUDIES SHOULD INCLUDE INVESTIGATIONS IN ANIMALS AND IN MODEL SYSTEMS AS WELL AS IN MAN.

II

RESEARCH SHOULD BE DIRECTED TO FURTHER INVESTIGATION OF DISEASES PRODUCED BY SPECIFIC INFECTIOUS AGENTS BECAUSE SUCH STUDIES ARE LIKELY TO LEAD TO GREAT GAINS IN A RELATIVELY BRIEF INTERVAL.

1. Professional Activity Study: Hospital Discharge Data by Diagnosis, National Disease and Therapeutic Index. Ambler, Pennsylvania, unpublished data, 1971.

2. U.S. Public Health Service, Vital Statistics of the United States, 1968, National Center for Health Statistics, 1971.

3. U.S. Public Health Service, National Center for Disease Control, unpublished data.

4. Chanock, R.M.: Mycoplasma Infection of Man. New Eng. J. Med. 273: 1257-1264, 1965.

5. Austrian, R.: The Current Status of Pneumococcal Disease and the Potential Utility of Polyvalient Pneumococcal Vaccine. In *International Conference on the Application of Vaccines against Viral, Rickettsial and Bacterial Diseases of Man.* Pan American Health Organization Scientific Publication, Washington D.C. 226: 359-363, 1971.

6. Austrian, R., and Gold, J.: Pneumococcal Bacteremia with Especial Reference to Bacteremic Pneumococcal Pneumonia. Ann. Int. Med. 60: 759-776, 1964.

7. Kaufman, P.: Pneumonia in Old Age. Arch. Int. Med. 79: 518-531, 1947.

8. Hansman, D., Glasgow, H., Sturt, J., Devitt, L. and Douglas, R.: Increased Resistance to Penicillin of Pneumococci Isolated From Man. New Eng. J. Med. 284: 175-177, 1971.

9. Kendrick, P.L., Gottshall, R.Y., Anderson, H.D., Volk, V.K., Bunney, W.E., and Top, F.H.: Pertussis Agglutinins in Adults. Public Health Rep. 84: 9-15, 1969.

10. Mores, S.I.: Pertussis in Adults. Ann. Int. Med. 68: 953-954, 1968.

11. Green, G.M.: Pulmonary Clearance of Infectious Agents. Ann. Rev. Med. 19: 315-336, 1968.

12. Albert, R.E., Lippmann, M., Spiegelman, J., Strehlow, C., Briscoe, W., Wolfson, P., and Nelson, N.: The Clearance of Radioactive Particles From the Human Lung. In *Inhaled Particles and Vapours II.* ed. C.N. Davies. Pergamon Press, Oxford, pp. 361-378, 1967.

13. Toigo, A., Imarisio, J.J., Murmall, H., and Lepper, M.: Clearance of Large Carbon Particles From the Human Tracheobronchial Tree. Amer. Rev. Resp. Dis. 87: 487-492, 1963.

14. Green, G.M., and Kass, E.H.: The Role of the Alveolar Macrophage in the Clearance of Bacteria From the Lung. J. Exp. Med. 119: 167-176, 1964.

15. Ouchi, E., Selvaraj, R.J., and Sbarra, A.J.: The Biochemical Activities of Rabbit Alveolar Macrophages During Phagocytosis. Exp. Cell Res. 40: 456-468, 1965.

16. Gee, J.B. ., Vassallo, C.L., Bell, P., Kaskin, J., Basford, R.E., and Field, J.B.: Catalase-Dependent Peroxidative Metabolism in the Alveolar Macrophage During Phagocytosis. J. Clin. Invest. 49: 1280-1287, 1970.

17. Green, G.M. and Goldstein, E.: A Method for Quantitating Intrapulmonary Bacterial Inactivation in Individual Animals. J. Lab. Clin. Med. 68: 669-667, 1966.

18. LaForce, M., Kelly, W., and Huber, G.: Stimulation of Bactericidal Activity of Alveolar Macrophages with Surfactant. Clin. Res. 20: 579 a, 1972.

19. Green, G.M., and Carolin, D.: The Depressant Effect of Cigarette Smoke on the *In Vitro* Antibacterial Activity of Alveolar Macrophages. New Eng. J. Med. 276: 421-427, 1967.

20. Goldstein, E., Green, G.M., and Seamans, C.: The Effect of Acidosis on Pulmonary Bactericidal Function. J. Lab. Clin. Med. 75: 912-923, 1970.

21. Lourenco, R.V., Stanley, E.D., Gatmaitan, B., and Jackson, G.G.: Abnormal Deposition and Clearance of Inhaled Particles During Upper Respiratory Viral Infections. J. Clin. Invest. 50: 62a, 1971.

22. Morrow, P.E., Gibb, F.R., and Gazioglu, K.: The Clearance of Dust From the Lower Respiratory Tract of Man: An Experimental Study. In *Inhaled Particles and Vapours II.* ed. C.N. Davies. Pergamon Press, Oxford, pp. 351-359, 1967.

PANEL IX

PULMONARY VASCULAR DISEASES

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PULMONARY VASCULAR DISEASES

The report of the panel on Pulmonary Vascular Diseases is in four parts:

Cor Pulmonale

Pulmonary Hypertension

Pulmonary Edema

Pulmonary Embolism

These diseases were selected because they warrant attention by virtue of their importance as national health problems, and because they relate to diseases studied by other panels of the Task Force.

INTRODUCTION

Cor pulmonale is cardiac enlargement resulting from diseases primarily affecting either the structure or function of the lung. This definition is similar to the one adopted by an expert committee of the World Health Organization (1). A clinical definition cannot be entirely satisfactory because the major clinical manifestation is heart failure, which may be long delayed and perhaps only the terminal event. A functional definition in terms of pulmonary hypertension or elevated pulmonary vascular resistance is also unsatisfactory: the pulmonary hypertension may be intermittent and pulmonary vascular resistance is relatively difficult to measure. However, this should not discourage attempts to develop better methods to diagnose cor pulmonale during the course of the disease rather than at autopsy.

A large number of diseases affecting the pulmonary circulation impose a chronic increase in work load on the right ventricle that may result in hypertrophy and ultimately right ventricular failure. These diseases fall into three groups:

- -Conditions primarily affecting the ventilatory and respiratory functions of the lungs. The clinical picture is dominated by the causative lung disease; pulmonary failure precedes cardiac failure.

- -Conditions acting directly on the pulmonary blood vessels. When cardiac failure precedes pulmonary failure, pulmonary function is not usually seriously disturbed.

- -Primary cardiac diseases. The clinical picture is initially dominated by the primary cardiac lesion.

It is only in the first two groups that the primary impact of the disease process is on the lung; such conditions may therefore be regarded as possible causes of cor pulmonale. Certain congenital heart lesions, and conditions primarily affecting the left side of the heart, may also exert secondary effects on the lung. Such conditions, however, are excluded as causes of cor pulmonale by the panel's definition. Right ventricular hypertrophy is the only lesion that is common to all patients at all stages of cor pulmonale. This excludes secondary effects on the right ventricle that may arise from acute lung diseases in the course of a few days or weeks.

Subjective evaluations of ventricular hypertrophy or assessments by measurement of mural thickness are unacceptable because minor degrees of hypertrophy may be masked by cardiac dilatation and it is impossible to compare observations made by different observers. It is essential to employ the more exact method of dissecting the ventricles apart and weighing them separately. In the most satisfactory and least time-consuming method so far described (2), the epicardial fat is removed and the atria are detached and weighed. The free wall of the right ventricle is separated from the interventricular system and weighed. The left ventricle and the attached interventricular septum are weighed together. The criterion for right ventricular hypertrophy based on this technique is a right ventricular weight of 80 grams or more. The criterion for left ventricular hypertrophy is a left ventricular weight greater than 225 grams.

MAGNITUDE OF THE PROBLEM

Accurate figures are unavailable on the national incidence of cor pulmonale or on its associated morbidity and mortality. However, a clue to its impact on national health may be found in figures available on chronic bronchitis and emphysema, discussed in the report on these diseases.

The major causes of cor pulmonale are undoubtedly chronic bronchitis and emphysema, although the frequency of its occurrence in these diseases is not accurately known. One study (3) reports right ventricular hypertrophy in 35.7% of 140 cases of emphysema examined at autopsy; another, more recent, study (4) reports right ventricular hypertrophy in 48.7% of 41 cases. Overall, it may be estimated that cor pulmonale occurs in 40% of cases of emphysema and chronic bronchitis.

Hospital autopsy records vary widely in the reported prevalence of cor pulmonale; reports range from 0.9% of all cardiac autopsies in Massachusetts to 54% in Arizona (1). Data from clinical discharges and autopsy services at three hospitals studied by the panel indicate that cor pulmonale might be present in 0.4% of discharges. Extrapolating to the 30.8 million hospital discharges in the United States during 1969 (5), there might be 123,000 cases of cor pulmonale. Estimating an average of 14 days hospitalization at a cost of $120 per day, the total national cost of hospitalization for patients with cor pulmonale would be approximately $200 million annually. This, of course, would overlap with cost estimates for chronic bronchitis and emphysema.

CURRENT STATE OF KNOWLEDGE

Pathogenesis

That cor pulmonale is associated with severe chronic bronchitis and emphysema has been well established by studying cardiovascular

abnormalities in patients with chronic respiratory diseases. One study (6) of 50 such patients has shown that those with mild obstructive ventilatory insufficiency, low-normal levels of cardiac output at rest and normal pulmonary arterial pressure at rest but mild pulmonary hypertension after light exercise, have normal blood-gas values, no clinical or electrocardiographic evidence of right ventricular hypertrophy, and a good prognosis. Patients with more severe obstructive ventilatory impairment, abnormally low levels of cardiac output and pulmonary hypertension during exercise, are also unlikely to be diagnosed clinically as "cor pulmonale" because electrocardiographic evidence of right ventricular hypertrophy, cardiomegaly and congestive heart failure are relatively infrequent. This pattern of cardiovascular dysfunction usually occurs in patients with the emphysematous form of chronic obstructive lung disease. As a result of the low cardiac output, tissue hypoxemia may develop and account in part for the severe weakness of many of these patients and their poor prognosis. Patients with the bronchitic type of chronic obstructive lung disease, severe hypoxemia usually associated with chronic hypercapnia, normal or even increased cardiac output and resting pulmonary hypertension, are likely to show clinical and electrocardiographic findings ascribed to "cor pulmonale". This pattern of cardiovascular abnormality is associated with a poor prognosis.

Other types of parenchymal lung disease in which cor pulmonale might play an important role (e.g., pneumoconiosis) have been only superficially investigated.

As cor pumonale is most frequently a consequence of chronic bronchitis and emphysema, studies of its pathogenesis will draw upon what is known about the pathogenesis and physiopathology of chronic obstructive lung disease and emphysema.

For some years it has been suspected that the left ventricle may also be involved in responses of the heart to lung disease. Autopsy studies suggest an increase in left ventricular wall thickness (7). Patients have shown clinical, radiological, and hemodynamic evidence of left ventricular dysfunction in the presence of severe lung disease (8). On the other hand, in a study (9) of 12 patients with chronic obstructive lung disease, there was no evidence to support the concept of left ventricular dysfunction in cor pulmonale. Because the majority of patients with cor pulmonale are middle aged or elderly men, there is frequently co-existent systemic cardiovascular disease which may not be clinically evident. Left ventricular dysfunction in such patients may have a multifactorial basis.

There is still uncertainty and debate as to whether chronic hypoxia or reduction of the capillary bed is more important in the pathogenesis of cor pulmonale. This is a fundamental matter of practical importance as destruction of the pulmonary capillary bed is an irreversible lesion, whereas pulmonary vasoconstriction as a consequence of hypoxia is potentially reversible. This emphasizes the need to use pathologic

methods that permit a quantitative approach: It is essential to employ modern morphometric methods. Although available (10,11,12), these methods are not used widely enough. Protocols that use subjective grading of right ventricular hypertrophy and evaluation of emphysema are valueless. Quantitative histological methods should be used to measure the total internal surface area, number of alveoli, and number of capillaries in the lungs.

Models

Because right ventricular hypertrophy is part of the physiologic adaptation to chronic hypoxia resulting from prolonged residence at high altitude, high altitude research has a direct bearing on the understanding of cor pulmonale. However, it is important to note that the similarity is only relative: the hypoxic patient with chronic obstructive lung disease may have reduced pulmonary capillary bed, a condition that does not apply to residents at altitude. in fact, there is experimental evidence that in young animals chronic exposure to low oxygen tensions results in development of increases in alveolar, capillary, and tissue volumes (13,14).

Animal models of emphysema have been developed but they have not been useful for the study of cor pulmonale. In small animals such as the rat, emphysema produced by exposure to sulphur dioxide or by use of proteolytic enzymes is not associated with development of cor pulmonale. Ideally, an animal model should be large enough to permit use of invasive techniques to study the development of respiratory and hemodynamic changes, and the model should develop the right ventricular hypertrophy characteristic of human cor pulmonale. Such a model would also provide an opportunity for using quantitative pathologic techniques to evaluate the respective roles of reduction in alveolocapillary bed and alveolar hypoxia in the pathogenesis of cor pulmonale. Implantable devices for monitoring cardiac performance would permit serial studies of right and left ventricular function. An animal model of cor pulmonale would also be useful to screen potential pulmonary vasodilator drugs. Such studies might indicate whether or not the pulmonary hypertension represents a useful adaptation to the stress of disease. It is possible that in cor pulmonale secondary to parenchymal lung disease, the pulmonary hypertension actually improves the distribution of ventilation to perfusion inequalities, even at the expense of a burden to the right ventricle. Finally, such a model would permit studies of oxygen transport at the tissue level to help assess the clinical significance of the low cardiac output type of cor pulmonale found in patients with the emphysematous type of chronic obstructive lung disease.

CONCLUSIONS

I

At present, a definitive diagnosis of cor pulmonale can only be made at autopsy. Moreover, if the disease is to be adequately treated and prevented, its natural history must be known; this, however, requires serial hemodynamic studies. Because right heart catheterization does not lend itself to repeated use in the same patient or to wide-scale screening, less invasive techniques must be developed. Development of such techniques would also permit ancillary studies necessary to an understanding of the pathogenesis of this disease. For instance, since tissue hypoxia might be responsible for the poor prognosis for many patients with cor pulmonale, studies of oxygen transport at the tissue level are also needed. The investigation of abnormal right ventricular function and its interrelations with left ventricular malfunction might help to achieve a better understanding of myocardial failure.

Patients studied during life should be entered on a register and, upon their death, detailed pathological studies of the lungs and heart, and clinico-pathological correlations should be made.

Diagnostic tests based on techniques less invasive than right heart catheterization should be developed, if real progress is to be made in early detection and treatment of cor pulmonale. Longitudinal studies are also dependent on development of such tests.

II

The fundamental, still unanswered question about the pathogenesis of cor pulmonale is the relative roles of hypoxia and capillary bed reduction. Since human investigation on a large scale is contingent on development of new techniques, the answer to this important question depends on development of a suitable animal model. Such a model would have the additional advantage of permitting assessment of new techniques.

Because chronic bronchitis and emphysema are the most frequent causes of cor pulmonale, a suitable animal model of chronic obstructive lung disease accompanied by right ventricular hypertrophy should be developed. The animal used should be large enough to permit use of invasive techniques for serial hemodynamic studies.

RECOMMENDATIONS

Because cor pulmonale is most frequently a consequence of chronic bronchitis and emphysema, research approaches to cor pulmonale should draw upon the large number of patients with these predisposing diseases, as well as on animal models of emphysema.

I

LONG-TERM PROSPECTIVE STUDIES OF PATIENTS WITH EMPHYSEMA AND CHRONIC BRONCHITIS SHOULD BE UNDERTAKEN TO ELUCIDATE THE CLINICAL AND HEMODYNAMIC CHANGES IN THESE PATIENTS AND TO CORRELATE THEM WITH MORPHOMETRIC PATHOLOGIC ASSESSMENTS OF HEART AND LUNGS.

II

AN ANIMAL MODEL OF CHRONIC RESPIRATORY DISEASE THAT WILL PERMIT STUDY OF HEMODYNAMIC CHANGES SHOULD BE DEVELOPED.

III

THE DEVELOPMENT OF TECHNIQUES THAT WILL PERMIT SERIAL HEMODYNAMIC STUDIES OF PATIENTS SHOULD BE FOSTERED.

REFERENCES

1. World Health Organization. Chronic Cor Pulmonale. Technical Report Series No. 213. Geneva. 1962.

2. Fulton, R.M., Hutchinson, E.C., Jones, A.M.: Ventricular Weight in Cardiac Hypertrophy. Brit. Heart J. 14: 413-420, 1952.

3. Leopold, J.G., Gough, J.: The Centrilobular Form of Hypertrophic Emphysema and Its Relation to Chronic Bronchitis. Thorax. 12: 219-235, 1957.

4. Heath, D., Brewer, D., Hicken, P.: Cor Pulmonale in Emphysema. Charles C. Thomas. Springfield, Illinois. 1969.

5. National Center for Health Statistics, Health Services and Mental Health Administration. U.S. Dept. of Health, Education, and Welfare. 1970 (unpublished data).

6. Burrows, B., Kettel, L.J., Niden, A.H., Rabinowitz, M., and Diener, D.F.: Patterns of Cardiovascular Dysfunction in Chronic Obstructive Lung Disease. New Eng. J. Med. 286: 912-918, 1972.

7. Kountz, W.B., Alexander, H.L., Prinzmetal, M.: The Heart in Emphysema. Am. Heart J. 11: 163-172, 1936.

8. Rao, B.S., Cohn, K.E., Eldridge, F.L., Hancock, E.W.; Left Ventricular Failure Secondary to Chronic Pulmonary Disease. Am. J. Med. 45: 229-241, 1968.

9. Davies, H. and Overy, H.R.: Left Ventricular Function in Cor Pulmonale. Chest. 58: 8-14, 1970.

10. Weibel, E.R.: Morphometry of the Human Lung. Academic Press. New York. 1963.

11. Weibel, E.R.: Airways and Respiratory Surface. In *The Lung*, eds. A.A. Liebow, and D.E. Smith. Williams and Wilkins. New York. 1968.

12. Dunnil, M.S.: Quantitative Methods in Histology. In *Recent Advances in Pathology*, ed. S.C. Dyke, Series V. Churchill. London. 1968.

13. Burri, P.H. and Weibel, E.R.: Morphometric Estimation of Pulmonary Diffusion Capacity. II. Effect of PO_2 on the Growing Lung. Resp. Physiol. 11: 247-264, 1971.

14. Bartlett, D., Jr. and Remmers, J.E.: Effects of High Altitude Exposure on the Lungs of Young Rats. Resp. Physiol. 13: 116-125, 1971.

PULMONARY HYPERTENSION

INTRODUCTION

Pulmonary hypertension is characterized by the elevation of pulmonary arterial pressure markedly above levels usually accepted as normal. Although clinical signs and symptoms may indicate pulmonary hypertension, a definitive diagnosis can be established only by right heart catheterization.

Elevation of pulmonary arterial pressure, in the absence of cardiac or pulmonary diseases that might cause the elevation, is called "primary" or "idiopathic" pulmonary hypertension. In many patients, postmortem histologic sections of the lungs reveal recent or organized thrombi of small pulmonary arterial vessels. However, experienced pathologists are able to distinguish between cases of vasoconstrictive primary pulmonary hypertension that has been complicated by thrombosis, and cases of secondary pulmonary hypertension which are due to thromboembolism. The majority of cases described as primary pulmonary hypertension are in fact correctly characterized, and are not secondary to development of pulmonary embolism (1). Primary pulmonary hypertension is found in women with Raynaud's phenomenon, who frequently develop scleroderma (2); in persons at altitude who are exposed to low oxygen; and after ingestion of certain drugs and chemicals. Oral administration of plant alkaloids (3,4) to rats and monkeys leads to severe pulmonary hypertension and death from right ventricular failure. A recent epidemic of primary pulmonary hypertension in Europe has been ascribed to ingestion of an appetite-suppressing drug, Aminorex (5). However, it has not been possible to duplicate this condition in experimental animals, possibly because of species variation in pulmonary vasoreactivity (6).

Secondary pulmonary hypertension may be the consequence of a number of factors: (1) Obliteration of the pulmonary vascular bed in chronic obstructive lung disease, pulmonary fibrosis, or because of multiple pulmonary emboli; (2) Passive elevation of pulmonary arterial pressure because of congestive heart failure or pulmonary edema; (3) Elevation of pulmonary blood flow, for example in certain congenital heart diseases with left-to-right shunt; (4) Alveolar hypoventilation from chronic bronchitis, kyphoscoliosis, or obesity. (5) Neurogenic or humoral pulmonary vasoconstriction, as in certain cases of mitral stenosis.

MAGNITUDE OF THE PROBLEM

The prevalence of primary pulmonary hypertension is certainly underestimated because the diagnosis can only be established by right heart catheterization. It is noteworthy in this context that many patients studied by right heart catheterization show clinical features strongly suggestive of pulmonary hypertension. Patients with scleroderma, studied by right heart catheterization, demonstrate

mild to moderate elevation in pulmonary arterial pressure even when there is no clinical evidence of pulmonary hypertension (2). Auscultatory, roentgenographic, and electrocardiographic techniques generally can only detect severe grades of pulmonary hypertension.

In one study (1), primary pulmonary hypertension was found in 0.5 to 1% of right heart catheterizations and anatomic evidence was found in 0.15 to 0.2% of autopsies. In one hospital studied by the panel, eight of 45,563 patients discharged in 1970 and 1971 had primary pulmonary hypertension. Extrapolating to national figures for patient discharges in the United States, severe pulmonary hypertension would be found in about 6,000 cases. An additional 6,000 might be undiagnosed because the pulmonary hypertension was moderate.

On the basis of an average hospitalization cost of $120 per day and a stay of 14 days for the 6,000 diagnosed patients, the annual cost would be approximately $10 million.

There is no satisfactory treatment of pulmonary hypertension as such. Therapy is directed to management of right heart failure by the usual means.

CURRENT STATE OF KNOWLEDGE

Diagnosis

Assessment of pulmonary circulation by cardiac catheterization is not practical for screening early cases of pulmonary hypertension or for serial examination of established cases. More practical, non-invasive techniques are under investigation in a number of centers. The most promising technique for indirect measurement of pulmonary arterial pressure is the nitrous oxide plethysmographic determination of instantaneous pulmonary capillary blood flow (7). The conduction time of the pulmonary arterial pulse has been shown (8) to bear an inverse relationship to mean pulmonary arterial pressure. The method gives a very high correlation between calculated and measured mean pulmonary arterial pressure.

Other techniques which might permit indirect estimation of pulmonary arterial pressure by measurement of pulmonary arterial conduction time include fluorodensitometry (9) and gamma densitometry (10). By use of these methods, regional ventilation of areas as small as 3 cm in diameter can be estimated. During breath holding, it is possible to sense regional perfusion pulses. The conduction time from a point between the S wave of the electrocardiogram and the upstroke of the peripheral densitometric wave appears to be similar to the values obtained by the nitrous oxide plethysmographic method (10).

Measurement of pulmonary arterial blood volume is helpful in determining the presence of active or passive alterations in pulmonary

vasomotor tone when pulmonary blood flow also is altered by a pharmacologic stimulus. Its measurement in man has been accomplished by a method requiring the injection of an ether solution into the pulmonary artery (11). A less invasive technique which shows promise is injection of a gamma-emitting isotope into a vein and following its time-course by a scintillation camera. The values obtained with either method are similar (12).

Other ancillary methods which might be useful in widescale screening include measurement of pulmonary diffusing capacity and capillary blood volume (13). These parameters are generally, but not always, reduced in pulmonary hypertension. Although an increase of physiologic dead space to tidal volume ratio during exercise occurs in pulmonary vascular disease (13), this technique is not practical for screening because it involves insertion of an indwelling arterial catheter. However, methods for determination of arterial carbon dioxide tension from suitable sensors placed on tissues, if they become feasible, would eliminate this objection.

Pathophysiology

Promising clues to the pathophysiology of pulmonary hypertension are emerging from studies of smooth muscle, particularly vascular smooth muscle.

Recently, the way has been opened to define the ultrastructural pathology of smooth muscle. Improvements in preparatory techniques for high magnification electron microscopy are now utilized to study normal and diseased human vascular smooth muscle. This has led to observations that provide ultrastructural evidence essential to the development of a model of contraction in vertebrate smooth muscles (14). It has also been shown that the sarcoplasmic reticulum of vascular smooth muscle can function as a calcium store (15) and that its volume varies in different smooth muscles. As these variations are paralleled by differences in the stores of intracellular calcium, the pathophysiologic implications of this observation are of great importance. Calcium activates the enzyme system responsible for contraction in smooth muscles; it has been suggested that abnormality of intracellular and transmembrane calcium transport is a possible cause of essential hypertension (16). Hence, the possibility that hypertension (pulmonary or systemic) may be accompanied by ultrastructural changes (e.g., abnormal volume) of sarcoplasmic reticulum in vascular smooth muscle deserves to be explored.

Electron microscopic studies of drug action on mitochondria and sarcoplasmic reticulum should provide greater insight into the mechanism of action of pulmonary vasoconstrictors and vasodilators (and of bronchoconstrictors and bronchodilators as well).

In another approach, intracellular microelectrodes are now being applied to electrophysiologic studies in smooth muscle (17). Other useful technical advances have been the introduction of extracellular and improved intracellular techniques for measurement of smooth muscle membrane resistance and the application of voltage clamping to smooth muscle (18).

One of the most important results of the electrophysiological studies was recognition that the electrical properties of the membranes of normal smooth muscles from different sources of the same species show considerable variation. These differences include not only different morphology of the action potentials, but also complete absence of action potentials in certain types of smooth muscles.

Membrane electrical activity plays a major role in regulating smooth muscle contractility, and, if abnormal, may contribute to the pathogenesis of pulmonary and other hypertensive states. Hence, comparative electrophysiological studies on normal and diseased smooth muscle would be of interest. An understanding of the sensitivity (normal or abnormal) of pulmonary vascular (and also bronchial) smooth muscle to excitatory or inhibitory agents depends upon a thorough study of the electrophysiological effects of the lung. Immune reactions may affect the smooth muscle membrane indirectly, through release of histamine and other endogenous transmitters, or they may have a direct effect on the smooth muscle membrane, in a manner previously demonstrated in striated muscles (19). This question is also amenable to electrophysiological studies, as is the important regulatory effect of cyclic AMP on smooth muscle function.

Ion movements have been used to determine the effects of drugs on smooth muscle (17). Studies of ^{45}Ca fluxes may show whether abnormal calcium transport participates in diseases of pulmonary vascular (and bronchial) smooth muscle, and could clarify the mechanism of action of smooth muscle relaxants and excitatory agents. Membrane permeability to ions has been found to vary in at least one form of spontaneously hypertensive vascular smooth muscle (20). An extension of such experiments to pulmonary vascular smooth muscle and to other forms of hypertension would provide information about possible abnormalities of membrane permeability.

Exploration along these lines can provide important specific information about the role of smooth muscle in diseases of the lung, and can also provide information critically needed in other related fields: the first detectable atherosclerotic change occurs in vascular smooth muscle cells (21). Diseases of systemic and pulmonary vascular smooth muscle, the involvement of bronchial smooth muscle in asthma and other pulmonary diseases, and the extensive use of drugs with primary or side effects affecting vascular and visceral smooth muscle, present inter-related problems of great public health interest. These problems can be fruitfully explored through systematic studies of the basic properties of normal and abnormal smooth muscles.

Pharmacology

A variety of vasodilators of potential value in therapy of pulmonary hypertension have been under investigation. However, their therapeutic assessment has been hampered largely by the absence of appropriate non-invasive techniques for the assessment of pulmonary hypertension in patients in clinical trials.

The effect of prostaglandins on pulmonary circulation has received scant attention despite extensive investigations of these compounds by numerous workers over the past few years. It appears that some varieties of prostaglandin A and prostaglandin E are potent pulmonary vasodilators (22,23). Prostaglandin E_1 in particular has a relatively prolonged effect; at least two or three times as long as equivalent vasodilation produced by acetylcholine. Its action is independent from adrenergic receptors and it dilates both arteries and veins.

Beta-receptor stimulants recently introduced for the treatment of bronchial asthma also appear to have pulmonary vasodilator effects (24). If these agents or their analogs can be shown to be free of inotropic cardiac effect, they might be highly useful in treatment of pulmonary hypertension by virtue of the prolonged duration of their action.

Work in experimental animals, particularly the dog, indicates that normally there is strong alpha-receptor "tone" in the pulmonary vessels. Administration of phenoxybenzamine removes this tone and causes pronounced pulmonary vasodilation; an effect observed even when beta-receptors are simultaneously blocked. Thus it seems that the effect of alpha-receptors may be dominant in the normal state.

Bradykinin, a naturally occurring polypeptide, has no direct effect on the pulmonary vessels resistance in man despite its potent vasodilator effect on the systemic arterial circulation. However, if subjects are first made hypoxic, bradykinin causes pulmonary vasodilatation. In this respect, bradykinin is similar to acetylcholine in that a prerequisite for its action is heightened pulmonary vasomotor tone (24).

Polypeptides have recently been prepared from small intestine and lung and have been shown to have potent vasodilator action on both systemic and pulmonary circulations. They have a prolonged duration of action and cannot be blocked by hyoscine, propanolol, phenoxybenzamine or methylsergide. In dogs, they reduce or prevent the pulmonary hypertension that can be produced by breathing hypoxic mixtures (25,26). The polypeptide from small intestine might be responsible for some of the features of portal cirrhosis. Patients with cirrhosis do not show pulmonary vasoconstriction on breathing a mixture of 10% oxygen in nitrogen (27). This effect might be a consequence of excessive peptide, which is normally inactivated by the liver, but not by the cirrhotic liver. The presence of increased concentrations of this peptide in cirrhosis might explain other features

of the disease; for example, hyperventilation, peripheral vasodilation and increased cardiac output.

The role of cyclic AMP on the intact pulmonary circulation has not been studied. As cyclic AMP mediates the beta-adrenergic effect of hyperpolarization on strips of rabbit pulmonary smooth muscle (28), it might be a potent pulmonary vasodilator. This is a possibility worthy of investigation.

CONCLUSIONS

I

In many patients pulmonary hypertension is undiagnosed because at this time definitive diagnosis requires right heart catheterization. Noninvasive techniques presently available are amenable to use as diagnostic tools but they must be validated against data from right heart catheterization.

A study of non-invasive techniques for diagnosing pulmonary hypertension is needed. As these techniques must be validated against right heart catheterization, high risk groups should be used for such studies.

II

Ultrastructural pathology, electrophysiology, and ionic changes are now being studied in vascular smooth muscle by the most sophisticated techniques. These approaches hold great promise for an understanding of the mechanisms by which alterations in vascular smooth muscle may lead to pulmonary hypertension.

To capitalize on new approaches and techniques of great promise, pathophysiologic studies should be carried out on human pulmonary vascular smooth muscle.

III

There are a sufficient number of pulmonary vasodilators now available to warrant clinical trial of their usefulness in pulmonary hypertension. But such trials must await development of appropriate non-invasive techniques to assess pulmonary hemodynamics in patients.

Studies of vasodilators as potential therapeutic agents are needed, and clinical trials should be undertaken when appropriate non-invasive techniques for patient assessment are available.

RECOMMENDATIONS

The technology for intensive study of pathogenesis, natural history and treatment of pulmonary hypertension is at hand. But the availability of patients at any one center is presently insufficient to permit interdisciplinary studies of clinical problems associated with this disorder.

REFERRAL CENTERS SHOULD BE DEVELOPED WHERE ADEQUATE NUMBERS OF PATIENTS WITH PULMONARY HYPERTENSION CAN CAN BE STUDIED BY PRESENTLY AVAILABLE SOPHISTICATED TECHNIQUES.

RESEARCH PROGRAMS IN THESE CENTERS SHOULD BE INTERDISCIPLINARY AND ADDRESS FUNDAMENTAL AS WELL AS CLINICAL PROBLEMS. THESE CENTERS SHOULD SERVE AS A FOCUS FOR THE DEVELOPMENT OF CLINICAL TRIALS TO ASSESS CURRENT AND NEW ANTI-HYPERTENSIVE AGENTS.

REFERENCES

1. Wagenvoort, C.A. and Wagenvoort, N.: Primary Pulmonary Hypertension. A Pathologic Study of the Lung Vessels in 156 Clinically Diagnosed Cases. Circulation. 42: 1163-1184, 1970.

2. Sackner, M.A.: Scleroderma. Grune & Stratton. New York. 1966.

3. Kay, J.M. and Heath, D.: Crotalaria Spectabilis: The Pulmonary Hypertension Plant. Charles C. Thomas. Springfield, Illinois. 1969.

4. Kay, J.M., Heath, D., Smith, P., Bras, G., and Summerell, J.: Fulvine and the Pulmonary Circulation. Thorax. 26: 249-261, 1971.

5. Gurtner, H.P.: Pulmonary Hypertension Produced by Ingestion of Substances. Bull. Physio-Path. 5: 435-441, 1969.

6. Kay, J.M., Smith, P., and Heath, D.: Aminorex and the Pulmonary Circulation. Thorax. 26: 262-270, 1971.

7. Lee, G. de J., and DuBois, A.B.: Pulmonary Capillary Blood Flow in Man. J. Clin. Invest. 34: 1380-1390, 1955.

8. Reuben, S.R.: Compliance of the Human Pulmonary Arterial System in Disease. Circ. Res. 29: 40-50, 1971.

9. Kourilsky, R., Marchal, M. and Marchal, M.T.: Recording Respiratory Function by X-rays: Basic Principles. Thorax. 20: 428-434, 1965.

10. Cattrell, V.G., Franklin, D.H. and Kirkpatrick, A.E.: Gamma Densitometry in the Study of Ventilation and the Pulmonary Circulation. Clin. Radiol. 21: 396-402, 1970.

11. Sackner, M.A., Segel, N., Samet, P., and Atkins, N.: Estimation of Pulmonary Arterial Blood Volume, Lung Density and Tissue Volume in Man. Proc. Int. Union Physiol. Sc. 9: 487, 1971.

12. Herrera, C.E. and Lewis, M.L.: Human Pulmonary Arterial Volume. Clin Res. 19: 511, 1971.

13. Nadel, J.A., Gold, W.M., Burgess, J.H.: Early Diagnosis of Chronic Pulmonary Vascular Obstruction; Value of Pulmonary Function Tests. Am. J. Med. 44: 16-25, 1968.

14. Somlyo, A.P., Somlyo, A.V., Devine, C.E. and Rice, R.V.: Aggregation of Thick Filaments Into Ribbons in Mammalian Smooth Muscle. Nature. 231: 243-246, 1971.

15. Devine, C.E., Somlyo, A.V. and Somlyo, A.P.: Sarcoplasmic Reticulum and Excitation Contraction Coupling in Mammalian Smooth Muscles. J. Cell. Biol. 52: 690-718, 1972.

16. Somlyo, A.P. and Somlyo, A.V.: Vascular Smooth Muscle. II. Pharmacology of Normal and Hypertensive Vessels. Pharmacol. Rev. 22: 249-353, 1970.

17. Bulbring, E., Brading, A., Jones, A. and Tomita, T.: Smooth Muscle. Williams & Wilkins. Baltimore. 1970.

18. Anderson, N.C., Ramon, F. and Snyder, A.: Studies on Calcium and Sodium in Uterine Smooth Muscle Excitation Under Current-Clamp and Voltage-Clamp Conditions. J. Gen. Physiol. 58: 322-339, 1971.

19. Alonso-de Florida, F., del Castillo, J., Garcia, X. and Gijon, E.: Mechanism of the Schultz-Dale Reaction in the Denervated Diaphragmatic Muscle of the Guinea Pig. J. Gen. Physiol. 51: 677-693, 1968.

20. Jones, A.W.: Alterations in K-Accumulation and Permeation in Arterial Smooth Muscles From Spontaneously Hypertensive Rats (SHR). Fed. Proc. 31: 400, 1972.

21. Jones, R.J.: Evolution of the Atherosclerotic Plaque. University of Chicago Press. Chicago. 1963.

22. Hyman, A.L.: The Active Responses of Pulmonary Veins in Intact Dogs to Prostaglandins F_2 Alpha and E_2. J. Pharmacol. Exp. Therap. 165: 267-273, 1967.

23. Hauge, A., Lunde, P.K.M. and Waaler, B.A.: Effects of Prostaglandin E_1 Adrenalin on the Pulmonary Vascular Resistance (PVR) in Isolated Rabbit Lungs. Life Sciences. 6: 673-680, 1967.

24. Widimsky, J., Daum, S., Herzog, H.: Pulmonary Circulation. Progress in Respiration Research. 5. Karger. Basel. 1970.

25. Said, S.I., and Kitamura, S.: Vasoactive Polypeptide Dilates Pulmonary Vessels During Alveolar Hypoxia, Histamine Infusion of Air Breathing. Fed. Proc. 30: 380, 1971.

26. Said, S.I., Mutt, V., Kitamura, S.: Vasoactive Polypeptide From Hog Lung. Fed. Proc. 31: 308, 1972.

27. Daoud, F.S., Reeves, J.T., and Schaefer, J.W.: Failure of Hypoxic Pulmonary Vasoconstriction in Patients with Liver Cirrhosis. J. Clin. Invest. 51: 1076-1080, 1972.

28. Somlyo, A.V., Haeusler, G. and Somlyo, A.P.: Cyclin Adenosine Monophosphate: Potassium-Dependent Action on Vascular Smooth Muscle Membrane Potential Science. 169: 490-491, 1970.

PULMONARY EDEMA

INTRODUCTION

Pulmonary edema is a pathologic state in which there is abnormal extravascular storage of fluid in the lung. In the normal lung, fluid which leaves the extravascular space is removed by lymphatic and capillary drainage. Fluid accumulates within the lung when hydrostatic pressure in the pulmonary capillaries becomes greater than the plasma oncotic pressure, the capacity for lymphatic drainage is exceeded, or the permeability of pulmonary capillaries is increased.

With the methods presently available, pulmonary edema can only be detected clinically late in its course, making prompt therapy of the developing condition impossible, and contributing to its morbidity and mortality.

In this report only pulmonary edema of cardiogenic origin is considered; that is, edema consequent to pulmonary capillary or left atrial hypertension. Left atrial hypertension may be caused by 1) mitral valve disease, due to mitral stenosis, papillary muscle dysfunction, or mitral insufficiency; and 2) left ventricular failure, due to coronary artery disease, myocardial infarction, systemic arterial hypertension, aortic valve disease, or myocardopathy.

MAGNITUDE OF THE PROBLEM

The frequency of pulmonary edema is undoubtedly underestimated. It is not reported if it occurs during hospitalization and is coded only when reported as the admitting diagnosis. Moreover, many patients with mild pulmonary edema are treated in emergency rooms or at home. In two hospitals studied by the panel, pulmonary edema constituted 1% of the discharge diagnoses. Since many of these patients had co-existing acute myocardial infarctions or other systemic diseases, it is difficult to estimate the duration of hospital stay due to acute pulmonary edema alone. Extrapolating from the experience in these two hospitals, it is estimated that hospital cases in which the primary reason for hospitalization was pulmonary edema might approximate 300,000 a year, nationally. If the average hospital stay were one week, the cost would be about $30 million a year.

As cardiogenic pulmonary edema is mainly the consequence of either degenerative or rheumatic cardiovascular disease, estimates of the magnitude of the problem of pulmonary edema in terms of national health must take into account those cardiovascular diseases with which it is associated. Degenerative cardiovascular disease is the major cause of death in the United States today, and the complication of pulmonary edema undoubtedly contributes significantly to this mortality.

CURRENT STATE OF KNOWLEDGE

The critical problem at this time is detection of pulmonary edema early enough in its course to be amenable to treatment. Physical or chest roentgenographic examinations detect pulmonary edema only in its last stage. Even such sophisticated procedures as estimation of extravascular pulmonary water by indicator dilution are insensitive to the early accumulation of fluid (1,2). Development of techniques for early detection will hinge upon a thorough understanding of biochemical, structural, and dynamic properties of the lung, its vasculature and its fluids.

Detection of Lung Water

Under light microscopy, the earliest manifestations of excess fluid in the lungs are in the connective tissue that surrounds small vessels and airways. Ultrastructural observations indicate that excess fluid accumulates in the thick portions of the alveolar system, which are rich in connective tissue. But this early stage of pulmonary edema is undetectable by light microscopy. When widening of alveolar septae can be visualized by light microscopy it is a late manifestation of pulmonary edema (3,4).

If lung water content could be accurately measured, it might be used to detect early pulmonary edema. But methods presently available are too insensitive or too cumbersome to employ in clinical situations. The simultaneous determination of the pulmonary blood volume and the pulmonary extravascular water volume (1) is an invasive technique not technically suitable for widespread clinical use. Extravascular pulmonary water content correlates fairly well with total lung water content at autopsy. In experimental animals it measures constant fractions (approximately 50%) of the total, even in the presence of severe pulmonary edema (2). But disadvantages of the method are 1) the difficulty of handling radioactive materials; 2) blood loss (about 50 ml per determination); 3) lack of equilibration of tritium with all lung water in one passage (only 70% of pulmonary extravascular water volume is detected); 4) limited repeatability; and 5) delay involved in radioactive counting and calculation time.

A new double indicator dilution technique has been studied in dogs, using heat as the diffusible and blood conductivity as the nondiffusible indicator (5). This method shows promise because it (1) involves no blood loss; (2) has almost unlimited repeatability; and (3) measures more of the lung water than the tritiated water method. The major disadvantages are the pulmonary arterial thermistor catheter and rather large arterial catheter which must be used.

Pulmonary tissue volume, which parallels the extravascular pulmonary water space, can be estimated by various techniques. The procedures presently available are too complex for use in patients with pulmonary edema.

Pulmonary tissue volume can be estimated from the disappearance of nitrous oxide or acetylene by deeply inspiring one of these gases with helium as a tracer and determining its disappearance at zero time, before gas absorption by pulmonary capillary flow. The disadvantages of the method are that it is lengthy, requires multiple breath-holding times and a steady state (6). Uptake of nitrous oxide by lung tissue during a single inspiration can also be estimated by measuring the pressure fall within a body plethysmograph (7). However, this method in its present form is only suitable for research studies, as the subject is confined in a closed chamber and requires some degree of training.

A rapid rebreathing method (8) warrants further exploration in patients with pulmonary edema, as it is particularly applicable to patients who find it difficult to breath slowly or to hold their breath. Rebreathing, with rapid gas sampling, provides a continuous registration of gaseous uptake from the alveolar air, without need for multiple breath holds. With the introduction into pulmonary laboratories of rapidly responding gas analyzers, easily maintained mass spectrometers, and small digital computers, the rebreathing method for estimation of pulmonary tissue volume as well as diffusing capacity, capillary blood volume, capillary blood flow, oxygen consumption, and respiratory quotient becomes feasible, if the proper test gases are used.

A simple test that might be useful in following the development of pulmonary edema is the estimation of "closing volume." In pulmonary congestion and edema, a considerable proportion of small airways are closed at resting lung volume (9). However, a disadvantage of the method is that inspiratory and expiratory flow rates must be controlled at less than 0.5 liters per second, a maneuver that patients with congested lungs find difficult. Moreover, ultrastructural observations indicate that peribronchial edema is a rather late manifestation of pulmonary edema.

Another potentially useful technique to assess increases in lung water is estimation of transthoracic electrical impedence. This method is based upon the principle that the electrical impedence decreases as fluid replaces air within the chest. However, although simple conceptually, technical difficulties have precluded its clinical application (10).

Fundamental Studies

A study of alloxan-induced pulmonary edema in the dog (11) using tagged erythrocytes and albumin, suggests that detection of protein rather than water in the lung might be a more sensitive indicator of early pulmonary edema. Both red cell volume and albumin increase in the edematous lung, but protein accumulation seemed to occur earlier than capillary congestion.

In normal subjects studied by indicator dilution methods (1,12), pulmonary capillaries are relatively impermeable to sodium ions during the first circulation. However, patients with pulmonary insufficiency

following operation or injury show a significant loss of sodium. This loss probably represents sodium entry into a slowly exchanging compartment and might be correlated with the extent of pulmonary capillary damage.

The movement of macromolecules across the pulmonary capillary endothelium has been studied in isolated perfused lungs (13). When perfusion pressures were raised to produce pulmonary edema, tracers escaped from alveolar capillaries through interendothelial junctions into the interstitial space of the alveolar septum. The epithelial surface did not leak fluid unless perfusion pressures were raised much higher. This relative resistance of the epithelial, compared to the endothelial, surface to passage of water and solutes is not well understood. To determine whether mechanical stretching of the epithelium or accumulation of large quantities of protein in the interstitial space influences permeability requires further study (4).

Lipid analysis of the alveolocapillary membrane has largely concentrated on the role of surfactant in promoting alveolar stability. Alterations of lipid composition of the membrane in pulmonary edema might also affect its permeability characteristics.

Although edema fluid is relatively accessible in clinical pulmonary edema, little work has been done on its composition. In experimental pulmonary edema, the fluid has a high protein content, probably as a result of the balance of leakage of plasma from the blood vessels into the interstitial spaces and removal by lymphatics of plasma with lower concentration of protein. There is a higher content of albumin relative to globulin, but further electrophoretic characterization has not been performed (11). Scanty information is available on the non-protein constituents of edema fluid.

A summary (11) of the role of humoral and nervous mechanisms in the pathogenesis of experimental edema indicates that histamine release can adequately explain most of the events associated with edema formation; namely, increase in capillary permeability and increase in capillary hydrostatic pressure by venular constriction. An increase in vagal tone inhibits release of histamine, and vagotomy causes release and depletion of histamine from the lung. Capillary permeability also can be increased through stimulation of sympathetics to the lung by intracranial and hypothalamic foci. Bradykinin potentiates epinephrine-provoked experimental pulmonary edema.

Metabolic Effects of Pulmonary Edema

Metabolic studies have shown that the average uptake of oxygen by lung slices after alloxan-induced pulmonary edema is less than in controls (11). The lung is involved in a variety of metabolic activities, including detoxification, release and synthesis of vasoactive compounds such as prostaglandins, histamine, serotonin, and polypeptides. Alterations in lung metabolic activity as a consequence of pulmonary edema might have profound secondary effects on the lung itself and on other target sites.

CONCLUSIONS

Methods for early detection of pulmonary edema are urgently needed. In the absence of such methods, treatment begins too late to be effective in reducing morbidity and mortality. Many promising leads are available, but their development requires better understanding of the physiopathology of pulmonary edema.

Fundamental studies are needed as a first step to the development of sensitive methods for detecting pulmonary edema, methods that are suitable for use in patients and that will detect the disease early in its course.

RECOMMENDATIONS

PROGRAMS SHOULD BE FOSTERED FOR FUNDAMENTAL STUDIES ADDRESSED TO THE DYNAMICS OF EXCHANGE OF WATER, PROTEIN AND ELECTROLYTES, THE BIOCHEMISTRY OF EDEMA FLUID, AND METABOLIC ALTERATIONS IN THE EDEMATOUS LUNG.

THESE STUDIES SHOULD BE DESIGNED TO PROVIDE AN UNDERSTANDING OF THE PATHOPHYSIOLOGY OF PULMONARY EDEMA AS A STEP TO DEVELOPMENT OF SENSITIVE METHODS FOR ITS EARLY DETECTION.

REFERENCES

1. Chinard, F.P. and Enns, F.: Transcapillary Pulmonary Exchange of the Water in the Dog. Amer. J. Physiol. 178: 197-202, 1954.

2. Levine, O.R., Mellins, R.B. and Fishman, A.P.: Quantitative Assessment of Pulmonary Edema. Circ. Res. 17: 414-426, 1965.

3. Staub, N.C.: The Pathophysiology of Pulmonary Edema. Human Path. 1: 419-432, 1970.

4. Szidon, J.P., Pietra, G.G., and Fishman, A.P.: The Alveolar-Capillary Membrane and Pulmonary Edema. New Eng. J. Med. 286: 1200-1204, 1972.

5. Noble, W.H. and Severinghaus, J.W.: Thermal and Ductivity Dilution Curves For Rapid Quantitation of Pulmonary Edema. J. Appl. Phsyiol. 32: 770-775, 1972.

6. Cander, L. and Forster, R.E.: Determination of Pulmonary Parenchymal Tissue Volume and Pulmonary Capillary Blood Flow in Man. J. Appl. Physiol. 14: 541-551, 1959.

7. Sackner, M.A., Feisal, K.A. and Du Bois, A.B.: Determination of Tissue Volume and Carbon Dioxide Dissociation Slope of the Lungs in Man. J. Appl. Physiol. 19: 374-380, 1964.

8. Lewis, B.M., Lin, F.H., Noe, F.E. and Hayford-Welsing, E.J.: The Measurement of Pulmonary Diffusing Capacity for Carbon Monoxide by a Re-breathing Method. J. Clin. Invest. 38: 2073-2086, 1959.

9. Milic-Emili, J. and Ruff, F.: Effects of Pulmonary Congestion and Edema on the Small Airways. Bull. Physio. Path. Resp. 7: 1181-1196, 1971.

10. Severinghaus, J.W., Catron, C. and Noble, W.H.: A Focusing Electrode Bridge for Unilateral Lung Resistance. J. Appl. Physiol. 32.: 526-530, 1972.

11. Aviado, D.M.: The Lung Circulation, Vol. 11. Pergamon Press. Oxford. 1965.

12. Gump, F.E., Mashima, Y. Jorgensen, S. and Kinney, J.M.: Simultaneous Use of Three Indicators to Evaluate Pulmonary Capillary Damage in Man. Surgery. 70: 262-270, 1971.

13. Pietra, G.G., Szidon, J.P., Leventhal, M.M. and Fishman, A.P.: Hemoglobin as a Tracer in Hemodynamic Pulmonary Edema. Science. 166: 1643-1646, 1969.

PULMONARY EMBOLISM

INTRODUCTION

Occlusion of the pulmonary arterial tree in pulmonary embolism usually occurs from thrombi originating in peripheral veins or the right atrium. More rarely, it may be a consequence of obstructions from fat, bone marrow, cancer cells, foreign bodies, air, or other gases. Death in pulmonary embolism is almost always due to obstruction of the pulmonary circulation. There is no reliable evidence that reflex pulmonary vasoconstriction is of great significance in man; however, reflex bronchoconstriction and small airway closure may increase the severity of the symptoms. In the presence of congestive heart failure or pre-existing pulmonary emboli, even relatively small quantities of emboli may produce right heart failure, but in patients with normal cardiovascular and respiratory systems large quantities of emboli are necessary to cause right heart failure (1).

MAGNITUDE OF THE PROBLEM

It is difficult to diagnose pulmonary embolism accurately during life or to estimate the clinical significance of emboli found in the postmortem lung. Estimates of deaths range from 6,000 to 142,000 annually (2); a range reflecting the paucity of information about the natural history of this disease. Pulmonary embolism is believed to account for the hospitalization of about 300,000 patients a year in this country. It is said to be the most common lung complication of general hospital patients, and particularly for elderly patients immobilized for long periods (for example, after hip fracture).

Although under the best circumstances hospitalization of patients with pulmonary embolism should be about 14 days, a more realistic estimate of hospital stay is about four weeks. This disparity is a consequence of delays in diagnosis, difficulty in establishing therapeutic anticoagulant levels, and problems in evaluating post-emboli symptoms. Estimating an average daily cost of $100, hospitalization and physician care per patient would be $3,000. For 250,000 survivors, the total annual cost in this country might be $750 million. But these estimates do not include the very considerable economic burden of outpatient costs. These patients must take a daily drug, a weekly blood test for efficacy of anticoagulation, and weekly or monthly visits to an outpatient facility. The patient usually remains on oral anticoagulant for periods ranging from three months to life.

CURRENT STATE OF KNOWLEDGE

Prevention

At this time the major approach to the problem of pulmonary embolism is toward prevention. As clots arising from thrombosis of the deep veins of the lower extremity are the main source of pulmonary emboli, measures for preventing deep vein thrombosis in high risk patients are being studied.

Heparin in low doses holds considerable promise as a prophylactic measure in high risk groups. Several studies (5,6,7) of surgical patients indicate reduced incidence of postoperative venous thrombosis. One of these (6), a controlled study using I^{125} labelled fibrinogen scanning to detect venous thrombosis, reports a reduction of incidence from 41% to 15% in postoperative patients. Early data from another controlled study (8) of about 200 high risk patients shows that venous thrombosis (detected by I^{125} labelled fibrinogen) occurred in 3% of the treated group, in 25% of the randomized placebo group.

In another approach to prophylaxis, drugs that suppress platelet function are being investigated (9-12) to see whether they will prevent postoperative venous thrombosis. Controlled studies of aspirin (9) and dipyridamole (10) have not shown a beneficial effect. An uncontrolled study of aspirin (11) which did reveal a beneficial effect must be interpreted with caution as it is likely that aspirin masked the clinical signs of venous thrombosis, thus producing a deceptively low incidence in this group. The entire area of platelet-inhibiting drugs is under intensive study in several institutions. Theoretically, these agents would be expected to have an effect on the arterial circulation and perhaps not on the venous, but further evaluation is needed before firm conclusions can be drawn.

During the past few years, various methods (13-19) of preventing vascular stasis during surgery have been investigated for their effect on occurrence of postoperative venous thrombosis. While the results have varied, there is some evidence that if stasis is prevented by use of a pulsatile flow system postoperatively, venous thrombosis may be prevented.

Diagnosis

Non-traumatic methods that can be employed on a wide scale for accurate diagnosis of pulmonary embolism are not yet available. Such accurate diagnostic methods are essential to assess the efficacy of treatment and prophylactic measures.

The introduction of better procedures for diagnosis of pulmonary embolism than are currently available could be substantially aided by a primate model that mimics peripheral venous thrombosis and pulmonary embolism in man.

It is important to develop radioactive scanning procedures to tag the clot within the lung so that its identification is possible as a "hot spot." Studies of fibrin split products warrant further investigation as a diagnostic procedure. The wide scale use of I^{125} labelled fibrinogen is not at present possible in this country because of the risk of transmitting hepatitis, a risk that could be circumvented by careful screening of blood donors.

Therapy

Although other agents have been tried (20-23), heparin appears to be the most satisfactory anticoagulant in therapeutic use today. However, it has the disadvantages of being effective only by injection and of sometimes being erratic in controlling anticoagulation. A therapeutic approach presently under study is the use of fibrinolytic agents (24). The first phase of a cooperative trial of urokinase has not demonstrated efficacy in terms of either morbidity or mortality, but the obstructing thrombus undergoes lysis more rapidly in the urokinase group than in the heparin-control group. Pulmonary embolism is the model for a study now in progress comparing urokinase and streptokinase. However, heparin remains the treatment of choice pending proof that thrombolytic agents have a place in therapeutic management.

CONCLUSIONS

I

Non-traumatic methods that can be widely used and that will accurately diagnose pulmonary embolism are not available. In their absence it is not possible to assess adequately the efficacy of prophylactic and therapeutic measures presently available.

A suitable primate model for study of peripheral venous thrombosis would contribute substantially to the development of better diagnostic procedures. But their development also requires a comprehensive study of fibrinolysis, platelet function, and coagulation.

Development of suitable diagnostic procedures is essential to progress in prevention and therapy of pulmonary embolism.

II

Heparin appears to be the most satisfactory anticoagulant agent in use today, but its administration often results in erratic control of anticoagulation, it is only effective by injection, and there is no general agreement about heparin dosage schedules for adequate anticoagulation.

The greatest impact on the reduction of morbidity and mortality in pulmonary embolism would come from prevention of deep venous thrombosis in high risk patients. The most promising prophylactic measure in this group appears to be a low dosage heparin therapy. In the absence of diagnostic techniques suitable for wide-scale use, a practical approach to assess the efficacy of low dosage heparin therapy during a relatively short period might be to tabulate the deaths in those patients receiving heparin and those serving as controls. But such an investigation requires a large number of patients to obtain statistical significance and therefore must be a cooperative study involving many groups of investigators.

Though costly, a study that demonstrated the success of heparin in low doses might have a dramatic effect in reducing mortality from pulmonary embolism, particularly if it were possible to diagnose patients likely to develop a hypercoagulable state with stress and to institute prompt prophylaxis with anticoagulants.

When suitable diagnostic tests for pulmonary embolism are available, critical trials of the efficacy of therapy with low doses of heparin should be undertaken.

RECOMMENDATIONS

I

STUDIES SHOULD BE PROMOTED FOR DEVELOPMENT OF ACCURATE DIAGNOSTIC TESTS FOR PULMONARY EMBOLISM THAT ARE SUITABLE FOR WIDE-SCALE STUDIES IN HIGH RISK GROUPS.

II

WHEN SUITABLE DIAGNOSTIC TESTS ARE AVAILABLE, CLINICAL TRIALS OF HEPARIN IN HIGH RISK GROUPS SHOULD BE UNDERTAKEN.

REFERENCES

1. Marshall, R.: Pulmonary Embolism: Mechanism and Management. Charles C. Thomas. Springfield, Illinois. 1965.

2. Hume, M., Sevitt, S., and Thomas, D.P.: Venous Thrombosis and Pulmonary Embolism. Harvard University Press. Cambridge. 1970.

3. Morrell, M.T. and Dunnill, M.S.: The Post-Mortem Incidence of Pulmonary Embolism in a Hospital Population. Brit. J. Surg. 55: 347-352, 1968.

4. Kakkar,V.V., Raferty, E.B.: Selection of Patients With Pulmonary Embolism for Thrombolytic Therapy. Lancet. 2: 237-241, 1970.

5. Sharnoff, J.G. and DeBlasio, G.: Prevention of Fatal Postoperative Thrombolism by Heparin Prophylaxis. Lancet. 2: 1006-1007, 1970.

6. Williams, H.T.: Prevention of Postoperative Deep-vein Thrombosis With Perioperative Subcutaneous Heparin. Lancet. 2: 950-952, 1971.

7. Kakkar, V.V., Field, E.S., Nicolaides, A.N., Flute, P.T., Wessler, S. and Yin, E.T.: Low Doses of Heparin in Prevention of Deep-vein Thrombosis. Lancet. 2: 669-671, 1971.

8. Hirsch, J.: personal communication.

9. O'Brien, J.R., Tulevski, V. and Etherington, M.: Two *In-Vivo* Studies Comparing High and Low Aspirin Dosage. Lancet. 1: 399-400, 1971.

10. Browse, N.L., and Hall, J.H.: Effect of Dipyridamole on the Incidence of Clinically Detectable Deep-vein Thrombosis. Lancet. 2: 718-720, 1969.

11. Salzman, E.W., Harris, W.H. and DeSanchis, R.W.: Reduction in Venous Thrombo-Embolism by Agents Affecting Platelet Function. New Eng. J. Med. 284: 1287-1292, 1971.

12. Carter, A.E., Eban, R. and Perrett, R.D.: Prevention of Postoperative Deep Venous Thrombosis and Pulmonary Embolism. Brit. Med. J. 1: 312-314, 1971.

13. Flanc. W., Kakkar, W. and Clarke, M.B.: Postoperative Deep-vein Thrombosis Effect of Intensive Prophylaxis. Lancet. 1: 477-478, 1969.

14. Tsapogas, M.J., Goussons, H., Peabody, R.A., Karmody, A.M. and Eckert,C.: Postoperative Venous Thrombosis & Effectiveness of Prophylactic Measures. Arch. Surg. 103: 561-567, 1971.

15. Doran, F.S.A., White, M. and Drury, M.: A Clinical Trial Designed to Test the Relative Value of Two Simple Methods of Reducing Risk of Venous Stasis in the Lower Limbs During Surgical Operations, The Danger of Thrombosis, and a Subsequent Pulmonary Embolus, With a Survey of the Problem. Brit. J. Surg. 57: 20-30, 1970.

16. Browse, N.L. and Negus, D: Prevention of Postoperative Leg Vein Thrombosis by Electrical Muscle Stimulation. An Evaluation with ^{125}I - Labelled Fibrinogen. Brit. Med. J. 3: 515-618, 1970.

17. Moloney, G.E., Morrell, M.T. and Fell, R.H.: The Effect of Electrical Stimulation of the Legs of Postoperative Thrombosis. Brit. J. Surg. 59: 65-68, 1972.

18. Dejode, L.E., Khurshid, M., and Walther, W.W.: Postoperative Leg Vein Thrombosis. Brit. Med. J. 4: 56, 1970.

19. Sabri, S. Roberts, V.C. and Cotton, L.T.: Prevention of Early Post-operative Deep-vein Thronbosis by Passive Exercise of Leg During Surgery. Brit. Med. J. 3: 82-83, 1971.

20. Sevitt, S. and Gallagher, N.G.: Prevention of Venous Thrombosis and Pulmonary Embolism in Injured Patients. Lancet. 2: 981-989, 1959.

21. Salzman, E.W., Harria, W.H. and DeSanchis, R.W.: Anticoagulation for Prevention of Thromboembolism Following Fractures of the Hip. New Eng. J. Med. 275: 122-130, 1966.

22. Pinto, D.J.: Controlled Trial of an Anticoagulant (Warfarin Sodium) in the Prevention of Venous Thrombosis Follwing Hip Surgery. Brit. J. Surg. 57: 349-352, 1970.

23. Hamilton, H.W., Crawford, J.S., Gardiner, J.H. and Wiley, A.M.L.: Venous Thrombosis in Patients with Fracture of the Upper End of the Femur. J. Bone Joint Surg. 52B: 268-289, 1970.

24. Urokinase Pulmonary Embolism Trial: Phase 1 Results; A Cooperative Study. JAMA. 214: 2163-2172, 1970.

PANEL X

RESPIRATORY DISTRESS SYNDROMES

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RESPIRATORY DISTRESS SYNDROMES

INTRODUCTION

The concept of acute respiratory distress as a syndrome or group of related syndromes is relatively recent, although the various illnesses or incidents that precipitate the syndromes have been known for a number of years. In some of these illnesses, such as aspiration pneumonia, "hyaline membrane" disease and severe pulmonary contusion, the aspect of acute respiratory failure was well recognized but incompletely understood. In other injuries and illnesses, such as shock, fat embolism and septicemia, the respiratory component was long overlooked.

The past 15 years have seen a tremendous advance in knowledge in this field. The advent of reliable and simple instrumentation for blood gas analysis and the increasing use and sophistication of respirators have allowed physicians to recognize and treat respiratory failure. This in turn has stimulated research into areas of etiology, physiology, pharmacology, pathology, biochemistry and therapy of the group of diseases addressed in this report: the respiratory distress syndromes (RDS). Although what constitutes respiratory distress syndromes is usually clear to investigators and clinicians working in the field, its meaning is unclear to the great majority of physicians, including some specializing in pulmonary disease. The panel has defined the syndromes generally as acute respiratory failure and distress associated with a specific incident or illness, with the exclusion of exacerbation of chronic lung disease. For purposes of this report, the following conditions, when associated with acute respiratory failure, are included under RDS:

-Infantile RDS
-Traumatic Wet Lung (also, Shock Lung)
-Fat Embolism
-Post-Perfusion Lung
-Disseminated Intravascular Coagulation
-Aspiration Pneumonitis
-Viral Pneumonia
-Septicemia
-Acute Renal Failure
-Burns
-Smoke or Gas Inhalation
-Drug Overdose

-Immunosuppression
-Oxygen Toxicity
-Long-Chain Hydrocarbon Ingestion
-Radiation
-Neurogenic Pulmonary Edema
-Fluid Overload

Conditions that may resemble RDS, but are specifically excluded in this report are as follows:

-Acute Cardiac Pulmonary Edema
-Acute Bacterial Pneumonia
-Acute Hypersensitivity Lung Disease
-Chronic Interstitial Fibrosis
-Goodpastures Syndrome
-Acute Exacerbations of Chronic Lung Disease

The panel recognizes that others might compile a somewhat different list. Categories such as neurogenic pulmonary edema are included in RDS because the basic mechanism is as yet incompletely understood. Cardiogenic pulmonary edema is excluded even though it may closely resemble RDS. The major reason for excluding it is to draw a distinction between pulmonary edema of cardiac origin and pulmonary edema which is secondary to primary pulmonary injury or pathology.

The patients present with a relatively acute onset related to a specific illness or injury. The clinical signs in both infants and adults are those of respiratory distress. The patient is dyspneic with tachypnea, grunting expiration and, frequently, intercostal and suprasternal retractions. Cyanosis is present and the clinical response to oxygen administration is poor. In neonates, prematurity is almost invariably present. Auscultatory as well as radiologic findings are often minimal or absent early in the syndrome. If left untreated, respiratory failure is progressive and death is precipitated by acute hypoxemia.

Radiologic findings in patients with RDS are as follows:

-Minimal or absent findings in early stages
-Diffuse bilateral alveolar infiltrates
-Air bronchogram

Physiologic findings are fairly well delineated as a consequence of considerable clinical investigation. While not all physiologic derangements occur in patients to the same degree, the general pattern is characteristic of the syndromes. Physiologic findings commonly associated with RDS are listed below:

-Increased minute ventilation
-Decreased functional residual capacity (FRC)
-Decreased lung compliance
-Low vital capacity
-Increased work of breathing
-Decreased surfactant activity (not rigorously proven)
-Increased physiologic shunt and $\dot{V}_A/\dot{Q}$ unevenness
-Hypoxemia
-Normal or low $PaCO_2$ in early stages, high $PaCO_2$ in late stages*
-Normal or high pH in early stages, low in late stages*

Pathologic findings are more difficult to categorize because, in general, pathologists do not recognize RDS, and also because the condition of the lungs at autopsy depends on whether or not the patient has had therapy. Ultrastructural changes associated with RDS in humans have not yet been studied, except in isolated instances. Therefore, only the gross and microscopic findings commonly seen in RDS are listed below:

Gross Findings at Autopsy:

-Adult patients dying acutely--deep red, heavy, relatively airless, congested lungs
-Infants--small, atelectatic, meaty lungs
-Late deaths after prolonged therapy--lungs may be small and fibrotic with emphysematous blebs

Light Microscopic Findings**

-Interstitial edema and congestion
-Intra-alveolar edema and hemorrhage
-Cellular proliferation (usually late)
-Fibrosis (late stages)

MAGNITUDE OF THE PROBLEM

For several reasons, valid statistical data to document the magnitude of the health problem due to RDS are virtually unobtainable: (1) Respiratory distress syndromes have only recently been recognized as such, and their definition has not yet been widely accepted. (2) Diagnosis and treatment of RDS depends primarily upon well-trained physicians in the community who can diagnose and treat patients properly. Relatively few hospitals outside of major medical centers have physicians who are specifically trained in acute respiratory care. (3) Respiratory distress syndromes are not included in current disease

*Primarily in adults
**Microscopic findings are commonly not homogeneous; structures appearing to be relatively normal may be adjacent to those showing severe pathology.

code classifications. Hence, meaningful statistical surveys of past experience are precluded, and future efforts to determine the extent of this illness will be hampered.

In an effort to obtain clues to the magnitude of the disease problem and the costs of care, some members of the panel collected data on their own or other institutions.* Although the panel addressed itself largely to RDS in the adult, data on care of neonates with RDS were also collected because they provide indications as to the magnitude of the syndrome, and as to the cost of intensive respiratory therapy.

A retrospective and prospective study of RDS in neonates, sponsored by the State of California in years 1968 through 1970 (1), showed that approximately 1% of all live babies developed neonatal RDS. In national terms, this means about 50,000 babies a year. Without specialized treatment, over 50% of these babies die. This mortality could be reduced to 42% in centers where specialized care was available, and could be further reduced to 10% in centers that were well staffed, well equipped, and used the newest techniques. Since approximately 75% of all perinatal deaths occur in premature babies, and since RDS is most likely to occur in premature neonates, if death from RDS could be reduced or eliminated, the infant mortality rate in this county might be reduced to a level among the best in the world.

The California study showed that the average cost of *minimal* care was $200 per patient. Where *intensive* care was provided, the cost averaged $3,500 per patient, and in centers with the best survival statistics the cost was $4,500 per patient. (These costs do not include physicians' fees.)

The panel also obtained data from eight large Army General Hospitals. One of these, devoted primarily to tuberculosis and care of chronic illness, is probably not representative. A second, served a large army training center and saw a high percentage of acute respiratory infections in otherwise healthy young recruits. The other six hospitals served a general population comprised of army personnel, retired military personnel, and dependents. Acute respiratory failure not associated with chronic lung disease was seen in 1,295 cases, with 377 deaths in one year. The number of cases of RDS was approximately 1% of the 127,000 admissions, and the deaths from RDS were approximately 25% of the 1,530 deaths that occurred in the hospitals during this period.

Although recognizing inaccuracies in these data, the panel believes them to be **representative of their own institutions as well as of other** institutions where physicians recognize the respiratory distress syndromes.

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*To maintain the confidentiality of these data, only summaries are presented in this report. The panelists' reports on their findings are in the files of the National Heart and Lung Institute.

The panel also obtained data from private hospitals representing over 4,650 beds. During a one-year period, 3,200 patients were seen with acute respiratory failure and roughly half of these were classified as RDS. Among the group of patients with RDS, there were 400 deaths; a mortality rate of 25%. As these figures were collected from hospitals with intensive care units and that were staffed by physicians well-trained in respiratory care, the data probably represent optimum care by present standards. In an earlier report (2), it was shown that, in the absence of treatment, mortality from RDS was greater than 70%.

The panel attempted to use data from the Committee on Professional and Hospital Activities, which serves as a repository for medical statistics from about one-third of the private hospitals in the United States. While data could be obtained for such diagnoses as fat embolism, acute viral pneumonia, septicemia and aspiration, it was not possible to determine from the data which patients developed acute respiratory failure. The data were not coded for either respiratory distress syndrome or acute respiratory failure.

One panel member compiled data for his hospital, showing that the average age of adult patients with RDS was 40 years. Data from infants and children were not included.

A conservative estimate of RDS in adults is 150,000 cases a year with an average mortality rate of 40%. In well-equipped, well-staffed hospitals, the cost of care is about $5,000 per patient. In assessing the impact of adult RDS as a national health problem, it should be stressed that the syndromes primarily affect young persons who are in their prime productive years; this presents a staggering economic loss to the nation. And in this context it should also be emphasized that RDS plays an important role in the morbidity and mortality resulting from severe accidental injury.

CURRENT STATE OF KNOWLEDGE

Recognition of RDS

To a great extent recognition of RDS depends on the astuteness and knowledge of the attending physician or nursing personnel. The panel believes that in many patients RDS is either not diagnosed or is recognized late in the course of disease. A lack of physicians trained in pulmonary or respiratory care, combined with inadequate care facilities and personnel in many community hospitals, hampers both recognition and treatment of RDS and almost certainly contributes to a much higher than necessary mortality.

Currently, recognition of RDS is based on clinical signs and symptoms, and the diagnosis is confirmed by increasing arterial hypoxemia (3,4). Roentgenographic findings are minimal in early stages and are not particularly helpful in making the diagnosis. At present

the best clinically available technique for early detection is serial monitoring of arterial blood gases in high risk patients.

Diagnostic tests which would lead to earlier detection and treatment would help greatly to reduce morbidity. Since the earliest pathologic manifestation of acute pulmonary injury appears to be accumulation of interstitial edema fluid and protein, a method which could detect early increases in lung water would be highly desirable. Ideally this method should be noninvasive, simple to perform, of low risk to the patient, reliable, repeatable, sensitive and relatively inexpensive.

Current approaches to this problem include radioactive tracer studies (5), thermodilution techniques (6), and transthoracic electrical impedance (7). But all of these current investigative approaches have serious limitations: tracer studies are complicated, time consuming, require considerable expertise and equipment, and do not lend themselves to multiple repetitions; thoracic impedance meets the requirements of simplicity, repeatability, noninvasiveness, low risk, and is relatively inexpensive, but as yet it is not sufficiently reliable or sensitive to be of clinical value; thermodilution techniques require some invasion of the patient's cardiovascular system, are relatively safe, reliable, repeatable and sensitive, but at present they require considerable expertise. Microelectrodes for continuous monitoring of arterial PO_2 are at present too expensive and fragile for routine use, are invasive, and do not discriminate edema formation from other causes of hypoxemia. While changes in functional residual capacity and in physiological dead space are found in advanced RDS it seems unlikely that these measurements would be sensitive enough to detect early edema formation (3).

Research in the area of recognition of RDS should be directed to the development of the ideal detector and monitor.

Mechanisms of Lung Injury

With the exceptions of aspiration pneumonia, direct trauma to the lung, and possibly fat embolism, little is known of the mechanisms of lung injury. A study has suggested that shock injures the lung by a relative ischemia during low flow periods. However, it has also been suggested that stasis with leukocyte aggregation and lysosomal release may be responsible for damage (8). Surfactant loss has been noted in adults with RDS, but it is not clear whether this is a cause or result of RDS. In infants, immaturity has been linked to surfactant production and to specific types of surfactant (9). Despite much study, the biochemistry of surfactant, its site of production, and its location in relation to the cell membrane are still areas of controversy. There is no simple biochemical test for its presence, absence, or degree of activity. Although the alveolar capillary

membrane seems to be the prime target site for injury, practically nothing is known about membrane physiology or biochemistry of the normal or injured lung.

Protective mechanisms against injury obviously are present, since not everyone in shock, sepsis or exposed to other causes of RDS develops the syndrome, and not all premature infants get into pulmonary difficulty.

Some experimental work indicates that repeated short exposures to high oxygen concentrations may have some protective effect against later prolonged exposure. The mechanisms of this protective effect are not known.

The role of *genetic or immunologic factors* which might protect or predispose to RDS is completely unknown. At the present time both approaches appear unpromising except as they relate to subsequent sepsis, which is discussed below.

The role of *vasoactive substances* in RDS, including prostaglandins, is incompletely understood. This area is discussed more completely in the report on pulmonary hypertension.

Platelet aggregation, intravascular coagulation, fat embolism, air embolism, amniotic fluid embolism and marrow embolism have all been demonstrated as causes of RDS. The mechanisms associated with multiple emboli and acute hemorrhagic edema are unclear. In fat embolism, the release of free fatty acids has been postulated, but this has never been proven conclusively (10).

Pathology

Pathologic studies of RDS at the electron microscopic level are few in number and are open to criticism since most are autopsy studies. It is unlikely that the pathologic development of RDS will be understood in humans unless a safe sequential biopsy technique can be developed. The use of high speed pneumatic drills offers some promise in this area, but the risk to the patient is still considerable. The benefits in terms of understanding of disease from both a biochemical and pathological standpoint might be enormous if more were known about the reaction of the human lung to injury. Similar studies need to be performed in animal models, but the primary need is in human pathology.

Therapy of RDS

Current therapy has concentrated on correction of ventilatory derangements and hypoxemia. The techniques used (volume respirator, large tidal volume, positive end-expiratory pressure and careful attention to inspired oxygen concentration) are based on physiologic derangements that are now relatively well understood (2,3,11,12). Little more is likely to be gained by stressing the physiologic

approach in investigation of RDS. This therapy is primarily valuable in preventing death from acute hypoxemia. As such, it has undoubtedly saved the lives of many patients whose underlying injury was self-limited or controlled by other therapeutic measures. In many other patients, especially in those with severe or continuing pulmonary injury, this therapeutic approach prolongs life but does not insure a successful outcome.

Pharmacologic approaches to correction of the underlying injury have consisted in attempts to remove water from the interstitial space of the lung, in the use of corticosteroids, and in the use of antibiotics to prevent infection. The use of salt-poor albumen combined with potent diuretics has shown much promise and has been studied in both animals and humans (13). Human studies, however, have not been controlled or extensive enough to prove the value of this method. Much of the effectiveness of this technique appears to be in the proper timing of its use. In the early stages of interstitial edema, the effects may be dramatic but little effect can be expected in late or terminal stages of RDS.

Corticosteroids have been used with considerable success in the treatment of fat embolism (14). While clinical opinion seems unanimous regarding their benefit, experimental evidence is lacking, and the method of action is only conjectural. In addition, controlled clinical trials have not been done. In aspiration pneumonia, animal experimentation has indicated that corticosteroids are useful and they appear to be useful in patients as well. But controlled studies are lacking. The use of corticosteroids in shock has been advocated on the basis of experimental evidence (4,15), but its value in patients is still unproven. The extreme difficulty in conceiving and executing controlled studies that involve critically ill patients with multiple problems will probably continue to act as a barrier to these and other pharmacologic studies in such patients. While pulmonary vasodilators have been used in infantile RDS, they have not been of particular value (16). They have not been evaluated in adults with RDS. It seems likely that new pharmacologic approaches will come only when there is a better understanding of the underlying mechanisms of injury.

Membrane oxygenators have undergone considerable investigation as a therapeutic method of sustaining life in RDS. While the early results were disappointing, recently successful outcomes have been reported after prolonged use of membrane oxygenators (17). This technique is very expensive in terms of personnel, equipment, and back-up facilities and at present remains a research technique. The limited number of patients who might benefit from this therapy, combined with its expense, will probably limit its application in the near future. However, it may eventually develop a role similar to that of extracorporeal bypass for cardiac surgery.

Repair Mechanisms

A small but significant number of patients with RDS survive the initial insult but then develop acute pulmonary fibrosis. The mechanism of this is not understood. Its intensive study could yield clues to the entire field of interstitial fibrosis. While oxygen has been blamed as the cause of interstitial fibrosis in these patients, this has not been proven unequivocally, and it seems likely from clinical observations that infection may play a more important role. Genetic factors may also play a significant role although at present they are entirely unknown. Research directions, as outlined in the panel report on interstitial fibrosis, may open a promising area that could lead to important therapeutic techniques.

The natural history of patients with RDS needs better delineation through long-term studies. While most patients that recover seem entirely well, reports on follow-up of these patients are nonexistent. It would seem important to obtain documentation on those patients who recover without permanent injury and those that are left with residual lung damage. A study of genetic and immunologic differences between these groups could yield important information.

Infections in RDS

Bacterial infection may precipitate or perpetuate RDS. The mechanisms are not clear, but endotoxins and septic shock have been implicated. More important in RDS, however, is the observation that the acutely injured lung is highly susceptible to secondary bacterial infection. While many reasons have been offered to explain this high incidence of infection, altered host defense mechanisms seem to play an important role. The pulmonary macrophage may be altered or its function impaired in acute pulmonary injury (18). The use of broad spectrum prophylactic antibiotics may destroy normal respiratory tract flora, allowing secondary invasion by highly resistant hospital organisms. This factor of sepsis in RDS demands immediate and further study as sepsis is now a leading cause of death in those RDS patients who survive the initial period of acute respiratory failure.

Approaches to this problem will revolve primarily around host and lung defense mechanisms although the role of antibiotics needs clarification, especially in the use of prophylactic antibiotics. The use of vaccine and hyperimmune plasma has had some success in prevention of infection in burn patients (19) and deserves a trial of RDS patients as well.

CONCLUSIONS

I

Current therapeutic approaches are capable of dramatically lowering morbidity and mortality from RDS. Their widespread application in

the general medical community would be a most valuable approach to lessening the impact of RDS in the future. But there is a lack of physicians, nurses, and technicians trained in respiratory care, both in the general medical community and in university centers. This need is likely to grow in the next five to ten years.

The most pressing need is for more trained personnel to apply presently known techniques and knowledge to the care of patients with RDS.

II

Physiologic alterations associated with RDS are now well understood, but little is known about the mechanisms of lung injury and repair. Fundamental problems requiring interdisciplinary studies include the following:

-Defense mechanisms of lung and host against injury and infection.

-Mechanisms and effects of edema formation in the lung, including studies of membrane structure and function, composition of edema fluid, better methods of early detection, and therapeutic measures to decrease edema fluid.

-Biochemical and ultrastructural changes that occur in the lung following injury from various agents.

-A search for factors that may predispose or prevent injury in the lung. Included here are growth and development, as yet unknown genetic factors, and the effect of prior injury on subsequent response.

-Repair mechanisms of the lung. Collagen metabolism including factors initiating collagen deposition and reabsorption, the migration of cells to the lung and the transformation of cells in the lung.

-Pharmacologic studies to identify drugs or compounds that may alter the natural course of pulmonary injury.

-A study of the natural history of patients recovering from RDS.

Basic research on the mechanisms of lung injury and repair provides the only approach to solving problems that currently hamper understanding and more effective treatment of RDS.

III

There are virtually no data on the incidence and prevalence of RDS or on morbidity and mortality associated with these diseases. Such data are necessary to provide baselines for determining trends in RDS. It is anticipated that as recognition of respiratory failure increases, the incidence reported will rise. Failure to diagnose, code and report patients with RDS hampers studies of natural history of the disease.

There is need for a uniform coding system for RDS and acute respiratory failure. This is an essential step to determining the magnitude of the national health problem of these disorders and to developing an effective research program addressed to them.

RECOMMENDATIONS

I

SPECIALIZED CENTERS SHOULD BE ESTABLISHED FOR TRAINING PHYSICIANS, NURSES AND TECHNICIANS IN ACUTE RESPIRATORY CARE.

WHERE FEASIBLE, CURRENT TRAINING PROGRAMS SHOULD BE EXPANDED, BUT NEW PROGRAMS SHOULD ALSO BE INITIATED FOR TRAINING IN THE CARE OF ACUTE RESPIRATORY FAILURE. TRAINING CENTERS SHOULD ALSO BE ESTABLISHED IN AREAS OF THE COUNTRY WHERE NONE ARE NOW AVAILABLE.

A CONSULTANT PROGRAM SHOULD BE ORGANIZED TO PROVIDE ADVICE, ON REQUEST, TO COMMUNITIES AND HOSPITALS DESIRING TO INITIATE PROGRAMS IN, AND TO DEVELOP FACILITIES FOR, CARE OF ACUTE RESPIRATORY FAILURE.

II

CENTERS SHOULD BE ESTABLISHED FOR BROAD, INTERDISCIPLINARY RESEARCH PROGRAMS ADDRESSED TO ACUTE PULMONARY INJURY.

THIS RESEARCH, BASIC IN NATURE, SHOULD INVESTIGATE THE PROTECTIVE MECHANISMS OF THE LUNG, THE RESPONSE OF THE LUNG TO INJURY, AND THE REPAIR MECHANISMS OF THE LUNG FOLLOWING INJURY.

III

THE STANDARDIZATION AND CODIFICATION OF RESPIRATORY DISTRESS SYNDROMES SHOULD BE PROMOTED. THIS STANDARDIZATION SHOULD BE WIDELY CIRCULATED TO THE GENERAL MEDICAL COMMUNITY AND ADDED TO CURRENTLY AVAILABLE MEDICAL CODIFICATIONS TEXTS.

THIS ESSENTIAL STEP SHOULD BE FOLLOWED BY A DETERMINATION OF THE INCIDENCE AND PREVALENCE OF RESPIRATORY DISTRESS SYNDROMES.

REFERENCES

1. A report to the 1971 Legislature on Hyaline Membrane Disease Pursuant to Chapter 1426, Statutes of 1968 (AB 1413, 1968) State of California, Department of Public Health, 1971.

2. Ashbaugh, D.G., Petty, T.L., Bigelow, D.B. and Harris, T.M.: Continuous Positive Pressure Breathing in Adult Respiratory Distress Syndrome. J. Thor. and Cardiovasc. Surgery. 57: 39-41, 1969.

3. Kumar, A., Falke, K.J., Geffin, B., Aldreidge, C.F., Laver, M.B., Lowenstein, E. and Pontoppidan, H.: Continuous Positive Pressure Ventilation in Acute Respiratory Failure. New Eng. J. Med. 283: 1430-1436, 1970.

4. Wilson, R.F., Asuncion, Z., Carrasquilla, C. and Lucas, C.: Respiratory Failure in Clinical Shock and Trauma. Current Topics in Surgical Research. 1: 361-374, 1969.

5. Gump, F., Mashima, Y., Jorgenson, S. and Kinney, J.M.: Simultaneous Use of Three Indicators to Evaluate Pulmonary Capillary Damage in Man. Surgery. 70: 262-270, 1971.

6. Gee, M.H.: The *in vivo* Volume of Pulmonary Fluid Compartments in Dogs and the Relationship Between These Volumes and the Hemodynamics and the Pulmonary Circulation. Ph.D. Thesis, University of Colorado, 1972.

7. Vandewater, J.M., Phillips, P.A., Thouin, L.G., Watanbe, L.S., and Lappen, R.S.: Bioelectric Impedance: New Developments and Clinical Application. Arch. Surg. 102: 541-547, 1971.

8. Young, W.G., Graham, T.C.: Leukocyte Changes in Pulmonary Circulation: A Mechanism of Acute Pulmonary Injury by Various Stimuli. Chest. 59: 36-39, 1971.

9. Gluck, L.: Pulmonary Surfactant and Neonatal Respiratory Distress. Hospital Practice. 6: 45-56, 1971.

10. Peltier, L.F.: An Appraisal of the Problem of Fat Embolism. Int. Abstracts of Surg. 104: 313-324, 1957.

11. Lutch, J.S., and Murray, J.F.: Continuous Positive Pressure Ventilation: Effects on Systemic Oxygen Transport and Tissue Oxygenation. Ann. Intern. Med. 76: 193-202, 1972.

12. Gregory, G.A., Kitterman, J.A., Phibbs, R.H., Tooley, W.H. and Hamilton, W.K.: Treatment of the Idiopathic Respiratory Distress Syndrome with Continuous Positive Airway Pressure. New Eng. J. Med. 279: 448-453, 1968.

13. Skillman, J.J., Parikh, B.M., and Tannenbaum, B.J.: Pulmonary Arteriovenous Admixture: Improvement with Albumen and Diuresis. Am. J. Surg. 119: 440-447, 1970.

14. Fischer, J.E., Turner, R.H., Hernden, J.H. and Riseborough, E.J.: Massive Steroid Therapy in Severe Fat Embolism. Surg. Gynec. Obstet. 132: 667-672, 1971.

15. Lillehei, R.C., Longerbean, J.K., Bloch, J.H., Manax, W.G.: The Nature of Irreversible Shock: Experimental and Clinical Observations. Ann. Surg. 160: 682-710, 1962.

16. Chu, J., Clements, J.A., Cotten, E., Klaus, M.H., Sweet, A.Y., Thomas, W.A. and Tooley, W.H.: The Pulmonary Hypoperfusion Syndrome. Pediatrics. 35: 733-742, 1965.

17. Hill, J.D., O'Brien, T.G., Murray, J.J., Dontigny, L., Bramson, H.L. Osborn, J.J. and Gerbode, F.: Extracorporeal Oxygenation for Posttraumatic Respiratory Failure. New Eng. J. Med. 286: 629-634, 1972.

18. Huber, G., LaForce, M. and Mason, R.: Impairment and Recovery of Pulmonary Antibacterial Defense Mechanisms After Oxygen Administration. J. Clin. Invest. 49: 47a, 1970.

19. Alexander, J.W., Fisher, M.W., MacMillan, B.G.: Immunologic Control of Pseudomonas Infection in Burn Patients: Clinical Evaluation. Arch. Surg. 102: 31-35, 1971.

PANEL XI

CARE OF ACUTE AND CHRONIC RESPIRATORY FAILURE

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CARE OF ACUTE AND CHRONIC RESPIRATORY FAILURE

INTRODUCTION

The sudden onset of respiratory symptoms and signs, and severe hypoxemia with or without hypercapnia, is defined as acute respiratory failure. Chronic respiratory failure is the presence of chronic respiratory symptoms with or without severe abnormalities of gas exchange.

The panel approached in broad terms the problems of care in these two types of failure and did not attempt to encompass all aspects of care of specific diseases.

MAGNITUDE OF THE PROBLEM

Although acute respiratory failure is an extremely common medical emergency associated with a variety of common medical disorders, information on its prevalence is virtually unobtainable. The eventual outcome of patients treated in either general hospital wards or in intensive care units is also not known. But some indications can be obtained from studies of survival of very ill patients with chronic obstructive pulmonary disease: treated in an intensive care unit, 65% of such patients survive. Data on the survival rate in general wards of hospitals are not available for comparison, but it seems reasonable to assume that survival would be considerably less. Data on survival after discharge are also virtually non-existent; one study (1) shows that 36% of patients were alive one year after discharge from a respiratory intensive care unit.

Reliable data on the prevalence of chronic respiratory failure are similarly unavailable. Estimates of the number of patients in this country with chronic respiratory disease, based on information from the insurance industry, the Veterans Administration, and the National Institutes of Health, range from 3 to 14 million. A survey of a number of chest physicians in this country and Canada (half in university-affiliated and half in community facilities) revealed that hospital admissions for treatment of chronic pulmonary disease ranged from 1 to 20 percent of all admissions. Estimates of chronic disability attributable to pulmonary disease ranged from 15 to 18 percent.

Mortality statistics indicate that chronic respiratory disease is a major cause of death in the older population, but these death statistics undoubtedly represent minimal estimates.

Neither the crude data on hospital admissions nor the mortality data provide an adequate measure of the health care problem or the economic impact of chronic respiratory disease: chronic obstructive pulmonary disease is probably considerably underdiagnosed. Hospital admissions represent only those patients most severely affected.

The disability of these patients for many of their most productive years, and the many hospitalizations required during exacerbations are not reflected in these data.

This lack of data regarding incidence, predisposing factors, etiology, and duration in hospital, highlights the importance of attempting to establish events antedating hospital admission of patients with acute respiratory failure.

Even in large centers there is little information on natural history and long-term follow-up of patients with chronic respiratory failure. Such information would help in answering a prevalent attitude among physicians that once an episode of severe hypercapnia ensues, the prognosis in chronic respiratory disease is uniformly poor. It is essential to learn the clinical, genetic, environmental, social, family, and occupational factors that have predictive value. Of equal importance are the immunologic, biochemical, physiologic, radiologic, and other laboratory features that can serve to identify patients who will survive following hospital admission. And survival should be assessed in terms of such indices as well being, length, quality and enjoyment of life, employment, etc.; not alone in terms of morbidity.

CURRENT STATE OF KNOWLEDGE

Chronic Respiratory Failure

As chronic respiratory failure is most common in patients with chronic obstructive pulmonary disease (COPD), this condition is used as a model for much of this section of the panel's report.

Because of the scarcity of research in the therapy of chronic respiratory failure, it is difficult to find careful, well-formulated investigations that clearly demonstrate the efficacy of various approaches to patient care. About one-third of the physicians surveyed by the panel expressed the rather strong view that none of the current therapeutic modalities for chronic pulmonary disorders have been adequately validated. To a large extent this is because studies are poorly controlled and they lack good standards for assessing success. Nevertheless, most of the physicians surveyed felt that bronchodilator therapy, antibiotics, measures directed at improving bronchial clearance (such as mist therapy and respiratory physiotherapy), as well as ventilatory assistance, had been adequately demonstrated to be effective when used in proper circumstances. Fewer expressed confidence in continuous oxygen therapy, breathing retraining, and rehabilitation measures. But this lack of confidence seemed in most instances to be based on the erroneous notion that the objective of the therapy was to reverse the disease and thus immediately alter the prognosis.

Unless specific infectious agents, or an immunologic or biochemical reaction, can be implicated, treatment of both acute and chronic respiratory failure is directed at physiologic abnormalities, and the principles

of management of these two conditions are similar. Most treatment is of transient benefit. There is no clearly documented evidence of its value in terms of disease progression, mortality reduction, or other factors that are important in the patient's ability to lead a useful existence. The current state of knowledge with regard to commonly used modes of therapy is briefly commented upon below.

Immunosuppressive therapy, predominantly with corticosteroids, is the non-specific treatment of choice in severe asthma which is not relieved by conservative therapy, in allergic interstitial pneumonitis, and in some collagen diseases and granulomatoses in which there are immunologic determinants. The role of steroids in COPD is still in question as there are few, if any, well-controlled studies. Steroids have been shown to be effective in some patients but not in others. In general, they are believed to be of value only when there is bronchoconstriction that does not respond to usual bronchodilator therapy, and are thought to be of no value in the patient with emphysema (2). Except for the occasional young patient with extrinsic asthma, the efficacy of hyposensitization therapy in asthma has not been satisfactorily demonstrated.

Bronchodilator therapy appears to be of transient value according to studies (3) in which bronchoconstriction was documented by clinical or physiologic methods. Its value in emphysema in the absence of bronchoconstriction has not been demonstrated. However, it may be of some prophylactic value in preventing airway construction caused by non-specific irritants. While additional studies on the effectiveness of bronchodilators are not likely to add much of value, there is a need for investigations on the best procedures for administering them. In addition, carefully controlled studies of the overall long-term role of bronchodilators are needed. Such studies should use standardized amounts and techniques of administration, and should be designed to determine the relation of bronchodilator therapy to physical therapy and other therapeutic modalities.

Treatment of heart failure in chronic respiratory insufficiency is controversial, although most physicians concede that digitalis and diuretics are of value when cardiac failure complicates chronic lung disease.

Treatment of infections with the appropriate antibiotic should be used when acute infection develops in patients with chronic respiratory disease. Antibiotics used prophylactically do not prevent recurrent infections but do lessen their severity. Empiric (broad-spectrum) antibiotic therapy may be clinically acceptable in management of chronic respiratory insufficiency when exacerbation of symptoms seems to be due to infection, but this has not been unequivocally established. Although gram-negative bacilli are commonly demonstrated in the sputum of patients with COPD, their role in the genesis and perpetuation of chronic bronchitis is unknown. Moreover, the role of viral infections has not been clearly identified.

Thinning of secretions with mucolytic aerosols may be of benefit when used intensively for short-term therapy, but for long-term use its clinical superiority over hydration by systemic and aerosol routes has not been demonstrated. Humidifying aerosols appear to be less effective than systemic hydration; there is no evidence that the chemical agents or enzymatic agents are superior. The clinical efficacy of expectorants or cough suppressants in chronic respiratory insufficiency has not been well studied.

Physical therapy in the management of patients with chronic respiratory disease is controversial. Theoretically, retraining in obstructive lung disease with slow and deep breathing should reduce the work of breathing. Some studies have demonstrated that by slowing respiration the oxygen-cost of breathing is decreased, but others show more efficient oxygen extraction at rest, and some slight improvement in ventilation-perfusion relationships. In general, physical therapy seems to have a positive effect on patients in that they report improvement in symptoms, but these effects might be related to the psychological benefits of increased activity. There are no properly controlled studies of the long-term effects of breathing retraining.

Postural drainage and pummeling increases the evacuation of sputum and reduces bronchial obstruction in acute respiratory infections or when bronchial secretions are retained. But specific benefits of postural drainage have not been documented for patients with COPD, except for its beneficial effects in localized airway disease (bronchiectasis).

Exercise training in patients with chronic airways obstruction has essentially the same physiologic effects as physical training in normal subjects. Investigations have shown that a program of daily graded exercises, sometimes with the necessary support of supplemental oxygen, results in an improved sense of well-being and often a significant increase in exercise tolerance (4,6). The improved capacity for exercise is accompanied by a reduction in cardiac rate and, if breathing retraining has been instituted, in a slowing of respiratory rate. But there is no improvement in respiratory function and the increased exercise tolerance may not carry over to other activities. The application of graded increase in activity to occupational or household chores (i.e. occupational therapy) has been virtually ignored. While there is no question that for some patients existence is improved considerably, there are no properly controlled studies which demonstrate that physical conditioning alters the course of the disease, morbidity, or mortality rate. The effects of physical conditioning in patients with chronic respiratory disease are difficult to distinguish from the effects of improved efficiency of performance of a given task, increased motivation, and lessened psychic stress. Documentation is needed to demonstrate whether physical conditioning has additional benefits.

Oxygen therapy is necessary in acute hypoxemia but its role in chronic situations is controversial. Certain patients with chronic airway obstruction may benefit significantly from supplemental oxygen therapy, particularly during exertion, but the studies demonstrating its benefit in improving a patient's exercise tolerance have been carried out primarily at an altitude of 5000 ft. (7). The role of continuous ambulant oxygen therapy should be evaluated at sea level, and there should be continued research into the role and long-term effects of oxygen administration in both acute and chronic respiratory failure.

Removal of irritants from the patients' environment is essential. The roles of environmental pollutants and cigarette smoking in chronic respiratory disease are amply discussed in reports of the panels on Environmental Diseases, and Non-Allergic Airways Diseases. The association between cigarette smoking and development of COPD has been well established and there is evidence that disability and absence from work is greater in bronchitics who continue to smoke. Although there is no evidence that progression of pathologic or physiologic abnormalities is slowed in patients with advanced disease, cough and sputum production are reduced or eliminated by cessation of smoking. Moreover, it has been demonstrated that dysfunction of small airways in asymptomatic smokers is reversible if smoking is discontinued. All therapeutic measures directed at COPD are over-shadowed by comparison with the effect that a moratorium on smoking or the development of the "safe" cigarette would have on this problem.

Publications aimed at altering the habits of the public (8,9), although produced by professional bodies as authoritative as is possible, have had little impact. Clinics for volunteer individuals have had significant failure rates. Stepwise increases in taxation of tobacco products have had only temporary effect in reducing overall consumption. However, there are some straws in the wind that the situation will improve: fewer physicians and dentists now smoke (10); the mortality from lung cancer is lower in men born in the 1920's than in men born in earlier decades of this century (11); the target population for cigarette manufacturers is now no longer teenagers but primarily young adults aged 23-45. Efforts should be directed toward identifying the psychological and pharmacologic factors leading to dependence on smoking, the most effective techniques for breaking this dependence, and the development of the safe cigarette.

Comprehensive long-term treatment programs doubtless prevent some early deaths from chronic respiratory disease and often allow the patient to function more effectively despite persisting disease (12,14). Home-care programs, in which there is continuous supervision by medical and paramedical personnel, can result in a significant reduction in hospital admissions and hospital days (15). However, it seems that function continues to deteriorate slowly with little, if any, effect on the excessive mortality rate (16). The few available assessments of comprehensive in-hospital and ambulatory care programs (which do seem to produce some initial subjective and objective improvement) have revealed disappointing results when viewed in terms of survival or alteration of progression of the disease (17).

To assess adequately the effectiveness of coordinated home-care services, models should include some of the following components: physicians' assistants, physiotherapy, home help, oxygen, nurses, social services and meals on wheels. Moreover, it is essential in such studies that the patients' conditions be comparable and that the endpoints of therapy be specified and measured. Endpoints should include prolongation of life, improved activities or daily living, and increased life satisfaction.

Studies are needed to evaluate the effectiveness of comprehensive care (including rehabilitation and home care) on patients with advanced lung impairment and disability. The few studies available indicate that early recognition, and management of exacerbations, may prolong the lives of some patients with advanced disease, but, in general, mortality has not been altered significantly. In this context it is noteworthy that although physicians surveyed by the panel indicated a great deal of skepticism about the impact of therapy, a surprising number of these physicians insisted that, on the whole, properly treated patients do not get progressively worse, except for the expected regression in function associated with aging.

Acute Respiratory Failure

The last decade has seen a broadening approach to acute respiratory failure. Major advances have been made in the techniques of diagnosis and care for acute respiratory insufficiency in hospital, and recommendations have recently become available on the essentials of an intensive respiratory care unit (18) and on the organization and staffing of intensive care units (19,20). Respiratory disease facilities are being centralized into one or more hospitals in a community, to provide a service for a defined population; and within the hospital the acute care of respiratory patients is being centralized in intensive care units.

The early recognition of respiratory failure and of acid-base disturbances has been greatly facilitated by the widespread use of blood gas electrodes. In some cases the device may have preceded and actually encouraged re-education of physicians. It is likely that increased use of blood gas analysis has resulted in earlier diagnosis of hypoxemia.

The principles of management of alveolar hypoventilation and associated problems are now well established (20,22). Earlier recognition and management of hypoxemia and hypercapnia resulting from disease of the airways, chest wall, neuromuscular system, or central nervous system, together with assisted or controlled ventilation when necessary, has resulted in a significant reduction in the mortality from this problem in many large centers.

Despite this encouraging aspect, it is apparent that advances in knowledge and their application to therapy have not been disseminated adequately to the more isolated or rural areas. In addition, even in

enlightened centers, the increasing use of blood gas analysis and artificial ventilation has resulted in a mechanistic approach to the problem, while underlying endobronchial infection, bronchoconstriction, and fluid retention may go untreated. Examples of problems warranting further study are commented upon below.

Infection continues to play a major role in the morbidity and mortality associated with acute respiratory failure. In addition to causing acute respiratory failure in patients with chronic lung disease, pulmonary infections can cause severe respiratory failure in previously healthy individuals; e.g. influenzal pneumonia, with or without superimposed staphylococcal pneumonia. Respiratory failure due to pneumonia carries one of the highest mortality rates of the patients in respiratory care units.

Studies are needed to determine factors that influence individual susceptibility to primary and secondary infection; for example, host defenses, interactions with other disease entities, macrophage inhibition, and the interaction of various antibiotics. In addition, methods should be developed to control secondary infection within a respiratory care area due to airborne contamination, transmission from patient to patient and from personnel to patient, and use of suction catheters and inhalation therapy equipment.

Cardiac disturbances should be studied to elucidate the mechanisms responsible for the apparent propensity toward cardiac arrhythmias in patients with acute respiratory failure. Such investigations should determine the precise nature of these arrhythmias and their relationship to the clinical conditions in which they occur, any associated conditions, the drugs which have been administered, and the status of acid-base and electrolyte balance, gas exchange, or other factors.

Burn injury needs investigation as little is known about the effects of combustion products of newer synthetic materials on the tracheo-bronchial tree and lungs. The effects of products of combustion of common household items should be studied in animals. The healing process should be documented so that guidelines for therapy in severely burned humans can be developed, particularly with regard to the role of infection and antibiotics, steroids, and cardiopulmonary bypass.

Aspiration pneumonitis should be studied to determine precisely the type of injury produced by aspiration. Most studies of aspiration relating to pH, use of steroids, antihistamines and other factors, have been done in a casual way and much remains to be answered. The reason for persistence of pulmonary abnormalities and respiratory failure in some patients, while others are left with little or no chronic pathology, is still unknown.

Oxygen toxicity is difficult to define in terms of morbidity and mortality because many patients undergoing oxygen therapy have also received a number of drugs or been exposed to therapeutic devices. The need for oxygen therapy in acute hypoxemia is well recognized. Different modes of administration have been evaluated, and several techniques for the administration of low concentrations of oxygen advocated. But when patients have received high concentrations of oxygen for a number of days the relation between the final pathologic picture and initial acute respiratory disorder is difficult to determine. It is possible that an animal model could be developed in which oxygen toxicity would be specifically produced, and the short- and long-term pathologic changes documented.

Adult respiratory distress syndrome and severe hypoxemia associated with shock, trauma, sepsis, myocardial infarction and post-operative patients, have become an increasing cause of fatal acute respiratory failure, but there is virtually nothing known about specific therapy. Many cases of hypoxemic respiratory failure are either directly iatrogenic or preventable (crystalloid overloading and aspiration) (21), yet there remains a large group where the lung damage is apparently secondary to another process. The major innovation in treatment of adult respiratory distress syndrome and related problems has been the use of continuous positive pressure breathing (23). Although the technique has been widely adopted, there is still not enough information on its effects in terms of cardiac output, oxygen transport, renal and cerebral function. It is probable that it is not a "cure" but merely an effective means of increasing lung volume and reducing the concentration of inspired oxygen to levels which do not produce pulmonary damage. Extracorporeal membrane oxygenators have also been used to "buy time" in this disorder, but thrombocytopenia still plagues these efforts. (Adult respiratory distress syndrome is discussed at length in the report of another panel.)

Respiratory monitoring is still in its infancy. Many physiologic and mechanical complexities are involved. The commonest cause of sudden death in patients on ventilators is mechanical obstruction or simple disconnect. The best respiratory monitor available today is a nurse at the bedside. As a consequence of inadequate staffing, inadequate facilities, and improper attitudes, many patients are left alone on ventilators, without proper attention or monitoring facilities.

Measurement of blood gas tensions, respiratory rate, tidal volume, and peak pressure on ventilators are extremely valuable in detecting changes in lung function, and yet these simple techniques frequently are not used. Spirometer alarms and low pressure alarms provide a simple and reliable way of monitoring for the common disasters, but they are seldom specified in criteria for intensive care units and are used infrequently in many hospitals.

Followup care of patients who have had an acute exacerbation of respiratory failure is being increasingly emphasized in order to prevent readmissions to hospital. Experience in several centers suggests that a home care program, actively pursued, can keep the patient with respiratory failure out of hospital. Wider experience with these programs is needed in order to assess their effect on mortality, morbidity, and the economics of health care.

As some patients seem destined to spend their remaining lives on ventilators, support and encouragement for the development of chronic respiratory care centers for this group of patients should also be considered.

Evaluation of Therapy

There are no studies of representative, large groups of patients, treated with different therapeutic modalities, which clearly demonstrate that the course of the disease is altered by treatment. Such studies are necessary but it is important to recognize that to evaluate a treatment regimen, the regimen must be standardized. Moreover, the natural history of the diseases being treated must be known in order to study the efficacy of therapeutic modalities in asymptomatic individuals with altered function, as well as in the symptomatic patient with respiratory insufficiency.

It is important to develop standardized methods of administration of therapeutic modalities. This would facilitate educating physicians in the principles of therapy and would also permit carefully controlled studies of efficacy of various therapies. In particular, pharmacologically-oriented studies, relating dose and response of various therapeutic agents, are needed. It would be advantageous to develop animal models of disease entities which lead to acute and chronic respiratory failure, and then utilize these models to assess the effects of known and new therapeutic approaches.

Equipment currently used for therapy should be evaluated, and new equipment should be developed in collaboration with biomedical engineers. Computer-assisted respiratory monitoring systems should be evaluated to determine whether the current high cost of this approach is offset by greater patient safety or better care. The role of sophisticated equipment, such as mass spectrometers and in vivo electrodes, must be carefully evaluated. Definitive reports on the evaluation of equipment for respiratory function testing, respiratory monitors, and ventilators would be of help to many of the less experienced.

Health Care Delivery for Respiratory Disease

It is clear that patients with respiratory disease are ill-served by episodic care, even by the specialist in respiratory disease. The major problem with care of respiratory disease in this country is its lack of organization: with some exceptions, it is still a "cottage industry." Patients have to make their own contacts with physicians, with no professional assistance in making their choice; frequently, no primary

physician is available in the community to provide continuity of care; and medical attention may be received in emergency rooms, outpatient clinics, or from specialists who are not always the appropriate specialist.

In addition, a great problem in the care of patients suffering from respiratory failure is the widening disparity between the knowledge and facilities available in the best university centers, and the almost total lack of facilities in some areas of primary patient contact. It is necessary to develop a system that will provide a continuum of care to these patients. It is recognized that such a development will not be easy, and indeed there may be no one system which is necessarily best, but any system developed for patient care should take into consideration the roles of family, primary physician , internist, chest specialist, nurse, nurse technician, respiratory technologist, physiotherapist, occupational therapist, inhalation therapist, social worker, psychologist, employer's health worker, the community hospital or clinics, and community health agencies.

Available Resources

Data on physical and professional resources for chronic respiratory care are scarce. Although there have been a few surveys of hospital resources, most of them have been conducted in areas where a state thoracic society was active and these probably reflect better-than-average resources. The majority of these surveys emphasize services and equipment but omit information on medical supervision and direction. The available information does not include the facilities and personnel for managment of chronic respiratory insufficiency, a condition which in many respects is more demanding and challenging than acute respiratory failure.

Facilities such as hospital beds, pulmonary laboratories, pulmonary therapy facilities or equipment for respiratory care range from excellent to almost non-existent. In part, the differences depend on availability of professional manpower, but in some instances the equipment and facilities actually preceded the manpower.

There are no national standards for resources for care of patients with acute and chronic respiratory insufficiency. These should be developed and included in hospitalization accreditation requirements. Many hospitals still attempt to manage patients with acute respiratory failure without proper facilities or staff.

Facilities for comprehensive care should be available to the patient with chronic respiratory insufficiency in each medical community, the depth and specialization depending upon the size and resources of the community. Massive programs for rehabilitation of patients with advanced respiratory insufficiency are probably not warranted at this time, but long-term care with supporting services, which would include home care and rehabilitation, could be provided by properly utilizing existing agencies and facilities.

Manpower trained in the pulmonary field are needed to meet present and growing demands for patient care. Preliminary data on the number of specialists trained in, and practicing in, pulmonary disease in this country indicate a considerable shortage of personnel in the practicing community and also to fill vacancies in positions that are already funded (24).

The shortage of pulmonary physicians per se is especially acute in view of the increase in pulmonary diseases as a health problem. The overwhelming demand by private medical facilities for trained pulmonary physicians to direct clinical pulmonary laboratories and respiratory therapy departments is reflected in the need for adequate faculty in pulmonary diseases.

The manpower problem is not one of numbers alone, but of maldistribution of service and inefficiency in utilizing existing manpower. It is necessary to educate the physicians who make first contact, to ensure early recognition of respiratory insufficiency, particularly in asymptomatic individuals. In addition, there is a great need for sufficient numbers of allied health professionals to work along with these physicians (25,27). "Physicians assistants," respiratory therapists, and physical therapists, inhalation therapy technicians and pulmonary function technologists, could be utilized in the recognition, prevention, and treatment of respiratory disease in the community.

Dissemination of Information

Dissemination of available information about acute and chronic respiratory care is inadequate. The extensive literature on the subject is reviewed at the discretion of the individual clinician or investigator and there is little exchange of methodology and experimental findings outside of annual meetings. The variety of specialties involved in respiratory failure research is great, and the diversity of meetings at which advances are reported precludes regular attendance. Dissemination of information has been largely the responsibility of individual local, regional, or national professional societies.

To meet national needs, exchange of information should go beyond interested specialties. Care of patients with respiratory failure is a matter of increasing importance to all practitioners as well as to community hospitals with critically ill patients. Emergency cases cannot be immediately transferred, hence all community hospitals should have personnel sufficiently informed for at least the initial resuscitation and management of acute respiratory failure. Training in this area is still haphazard. Since the needs of patients must often be met in the offices of primary physicians, internists, allergists, or others treating acute and chronic respiratory diseases, there is also need to educate these individuals in the use of available care modalities.

CONCLUSIONS

I

Knowledge presently available about the care of patients with chronic respiratory disease, or with threatened, intermittent or established respiratory failure, is not being adequately utilized in the care of patients. Despite the obvious need to gain new knowledge into many poorly understood aspects of respiratory failure, the most urgent need is the application of current knowledge, and improved delivery of health care to patients in the community.

The system of health care delivery for respiratory disease must be re-examined and developed to insure adequate care in community hospitals as well as in university centers.

Mechanisms are needed for dissemination of available information to community physicians and auxiliary personnel involved in care of patients with respiratory diseases.

Additional professional and auxiliary personnel are needed and they must be trained to deliver adequate respiratory care.

All hospitals must have minimal equipment and personnel necessary for immediate, emergency treatment of patients in respiratory failure.

II

Deficiencies in current knowledge are an impediment to the development of more effective ways of treating patients with acute and chronic respiratory diseases.

An understanding of the natural history of acute and chronic respiratory diseases, and reliable data as to their prevalence, are essential to the development and evaluation of effective modes of therapy.

Many therapeutic modalities in use today have not been adequately standardized or evaluated.

Controlled studies are needed to assess the efficacy of therapies presently in use.

Refinements of present models of therapy, and development of new ones, should be undertaken in collaboration with biomedical engineers.

Assessments of the effectiveness of therapy should be based on criteria that include the quality of life as well as morbidity and mortality.

RECOMMENDATIONS

I

CENTERS SHOULD BE DEVELOPED FOR CLINICAL RESEARCH AND PROFESSIONAL TRAINING IN THE MANAGEMENT OF RESPIRATORY FAILURE.

THESE CENTERS SHOULD EVALUATE METHODS OF CARE DELIVERY AND OFFER TRAINING AT THE COMMUNITY LEVEL. THEY SHOULD PROMOTE DISSEMINATION OF CURRENT AND NEWLY DEVELOPED INFORMATION.

THESE CENTERS SHOULD ALSO SERVE AS THE FOCUS OF STUDIES TO DETERMINE THE PREVALENCE OF ACUTE AND CHRONIC RESPIRATORY FAILURE.

II

INTERDISCIPLINARY RESEARCH PROGRAMS, USING CONTROLLED STUDIES, SHOULD BE FOSTERED TO DETERMINE THE EFFECTIVENESS OF EXISTING THERAPIES AND FOR THE DEVELOPMENT OF NEW THERAPEUTIC MODALITIES. THESE NEW REGIMENS SHOULD BE BASED ON AN IMPROVED UNDERSTANDING OF THE PATHOGENESIS OF ACUTE AND CHRONIC RESPIRATORY FAILURE.

REFERENCES

1. Moser, K: Personal Communication.

2. Pecora, L.J., Zoss, A.R., Baum, G.L, Kho, W. and Tan, A.: A Study of the Physiologic Effects of Intravenous Methylprednisolone in Chronic Pulmonary Emphysema. Amer. Rev. Resp. Dis. 89: 528-532, 1964.

3. Friedman, B.J. Bronchodilators and Corticosteroids in Chronic Bronchitis and Emphysema. Brit. Med. J. 2: 1509-1512, 1963.

4. Nicholas, J.J, Gilbert, R., and Gabe, P.: Evaluation of an Exercise Therapy Program for Patients with Chronic Obstructive Pulmonary Disease. Amer. Rev. Resp. Dis. 102: 1-9, 1970.

5. Pierce, A.K., Taylor, H.F., Archer, R.K. and Miller, W.F.: Responses to Exercise Training in Patients with Emphysema. Arch. Intern. Med. 113: 28-36, 1964.

6. Pierce, A.K., Paez, P.N. and Miller, W.F.: Exercise Training with the Aid of Portable Oxygen Supply in Patients with Emphysema. Amer. Rev. Resp. Dis. 91: 653-659, 1965.

7. Petty, T.L. and Finigan, M.M.: Clinical Evaluation of Prolonged Ambulatory Oxygen Therapy in Chronic Airway Obstruction. Amer. J. Med. 45: 242-252, 1968.

8. Royal College of Physicians of London. Smoking and Health. Pitman. London. 1962.

9. U.S. Public Health Service: Report of the Advisory Committee on Smoking and Health to the Surgeon General. PHS publication 1103 US Government Printing Office, Washington, D.C. 1964.

10. Steinfeld, J.L.: The Physician's Responsibility to His Smoking Patient. Rhode Island Med. J. 55: 119-123, 1972.

11. Adelstein, A.M.: The Medical Division of the Office of Population Census and Surveys. Health Trends. 4: 2, 1972. (London)

12. Petty, T.L., Nett, L.J., Finigan, M.M., Brink, G.A. and Corsello, P.R.: A Comprehensive Care Program for Chronic Airway Obstruction. Ann. Int. Med. 70: 1109-1120, 1969.

13. Petty, T.L.; Ambulatory Care for Emphysema and Chronic Bronchitis. Chest. 58: 441-448, 1970.

14. Burrows, B. and Petty, T.L.: Longterm Effects of Treatment in Patients with Chronic Airway Obstruction. Chest. 60: 25S-27S, 1971.

15. Cherniack, R.M., Handford, R.G. and Svanhill, E.: Home Care of Chronic Respiratory Disease. JAMA. 208: 821-824, 1969.

16. Burrows, B., and Earle, R.H.: Course and Prognosis of Chronic Obstructive Lung Disease. New Eng. J.Med. 280: 397-404, 1969.

17. Kimbel, P., Kaplan, A.S., Alkalay, L and Lester, D.: An In-Hospital Program for Rehabilitation of Patients with Chronic Obstructive Pulmonary Disease. Chest. 60: 6S-10S, 1971.

18. Petty, T.L. Dulfano, M.J., Singer, M. and Webb, W.R.: Essentials of an Intensive Respiratory Care Unit. Chest. 59: 554-556, 1971.

19. Safar, P. and Grenvik, A.: Critical Care Medicine: Organizing and Staffing Intensive Care Units. Chest.59: 535-547, 1971.

20. Cherniack, R.M., Cherniack, L. and Naimark, A.: Respiration in Health and Disease. (2nd edition). W.B. Saunders, Philadelphia, 1972.

21. Cherniack, R.M. and Kirk, B.W.: Acute Respiratory Failure. Current Therapy. W.B. Saunders, Philadelphia, 1972.

22. Bigelow, D.B., Petty, T.L. Ashbaugh, D.G., Levine, B.E., Nett, L.M. and Tyler, S.W.: Acute Respiratory Failure: Experiences of a Respiratory Care Unit. Med. Clin. N. Amer. 51: 323-340, 1967.

23. Ashbaugh, D.G., Petty, T.L., and Bigelow, B.B. Continuous Positive Pressure Breathing (CPPB) in Adult Respiratory Distress Syndrome. J. Thorac. Cardiov. Surg. 57: 31-41, 1969.

24. Survey of Professional Manpower in Pulmonary Diseases. National Heart and Lung Institute. 1972.

25. Morgan, R.H. Physician Assistants: Their Role in Medicine in the Years Ahead. J. Maine Med. Ass. 59: 219-223, 1968.

26. Riddick, F., Bryan, J.D., Gershenson, M.L. and Costello, A.C.: Use of Allied Health Professional in Internists' Offices. Arch. Int. Med. 127: 924-931, 1971.

27. Stead, E.A.: Training and Use of Paramedical Personnel. New Eng. J. Med. 277: 800-801, 1967.

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Task Force members are listed on page 3 and members of panels at the beginning of each panel report. In the following pages are names of members of the Panel on Fundamental Research Approaches and of Consultants to the Chairman.

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APPENDIX

ECONOMIC COSTS OF RESPIRATORY DISEASES

INTRODUCTION

The "economic costs of a disease" are estimates of the benefits that would accrue annually to the economy if the disease were eliminated or controlled; both morbidity (the condition of illness) and mortality contribute to these costs. Estimates include three components: direct costs due to illness; indirect costs due to morbidity; and indirect costs due to mortality. The methodology employed in determining these cost estimates has been described elsewhere (1).

> *Direct costs due to illness* are expenditures for prevention, detection, treatment, rehabilitation, research, training, and capital investment in medical facilities.
>
> *Indirect costs due to morbidity* are measured by the lost earnings associated with man-years lost in productivity as a consequence of illness or disability.
>
> *Indirect costs due to mortality* are measured in terms of the discounted present value of the life-time earnings of persons who died.

The respiratory diseases selected for purposes of this report are listed in Table A with their codes and terminology in the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD 7th Revision (2). They are grouped in terms of four major disease categories: inhalation (environmental) disease, disease of the airways, interstitial diseases, and vascular diseases. Data on these diseases are for year 1967, a year selected because the most complete relevant data were available for that year but not for more recent ones. (Table A)

The difficulties in obtaining reliable vital statistics are well known. In terms of this study several points should be made. Wherever possible, cost estimates are based on aggregate data for the entire United States rather than on cost-per-case studies. While such estimates have the advantage that they are based on a large number of observations, they also have the disadvantage that certain diseases are poorly defined and measured in aggregate data.

Table A

ICD Codes for Respiratory Diseases*

NHLI Task Force Terminology	Vital Statistics Terminology	Code
Inhalation Diseases		
Inorganic dusts	Pneumoconiosis due to silica and silicates	523
Noxious gases and organic dusts**	Other specified pneumoconiosis and pulmonary fibrosis of occupational origin	524
Diseases of the Airways		
Asthma	same	241
Bronchiectasis	same	526
Acute bronchitis	same	500
Bronchitis, chronic and unqualified	same	501,502
Pulmonary emphysema and bullous disease	Emphysema without mention of bronchitis	527.1
Cystic fibrosis	same	289A
Interstitial Diseases		
Collagen diseases	Other diseases of the arteries	456
Diffuse fibrosis	Other chronic interstitial pneumonia	525
Granulomatosis	Boeck's sarcoid	138.0
Bacterial pneumonitis	Lobar pneumonia and bronchopneumonia	490,491
Mycobacterial pneumonitis	Tuberculosis of respiratory system	001-008
Mycoplasma pneumonitis	Primary atypical pneumonia	492
Myctoic pneumonitis	Other infective and parasitic diseases	138.1
Viral pneumonitis	Influenza with pneumonia	480
Vascular Diseases		
Cor pulmonale and pulmonary hypertension	Kyphoscoliotic heart disease	434.0
Pulmonary edema	Acute left ventricular failure and acute heart disease, undefined	434.2 782.4
Thromboembolism	Pulmonary embolism and infarction	465
Hyaline membrane disease	same	773.0

*References 2,3

**Includes allergic interstitial pneumonitis

A number of diseases will be under-reported because they are often associated with other diseases more commonly reported as the primary cause of morbidity of death. For example, cor pulmonale secondary to curvature of the spine (kyphoscoliosis) is a coded item, but the ICD reporting greatly understates the magnitude of this disease, since a large portion is related to chronic bronchitis and obstructive lung disease. Similarly, inhalation diseases such as asbestosis will be understated when they have been a contributing factor to lung cancer, which will be the reported disease. Data on other diseases may be overestimated because the appropriate ICD code includes additional diagnostic categories. For example, Primary Atypical Pneumonia, code 492, includes several other unspecified causes of pneumonitis in addition to mycoplasma.

For some of the diseases, the cost estimates are incomplete. Data for allergic interstitial pneumonitis is included by the ICD with inhalation diseases and cannot be separated for presentation as an individual disease. In the case of respiratory distress syndrome in adults, no data exist as this disease is not yet coded as a separate item in the present reporting system.

Finally, some respiratory diseases, such as upper respiratory infections, hay fever, and lung carcinoma are excluded in computing these estimates since they are not within the purview of this Task Force Report. The first two of these conditions are associated with high morbidity and are some of the most important causes of loss of productive time by the working population, while lung carcinoma is increasing in incidence and generating a large indirect cost due to mortality. The addition of the economic costs of these conditions to that of the diseases specifically studied by the Task Force, increases even more the magnitude of the economic problem of respiratory diseases in the United States.

Despite shortcomings inherent in the data, the estimates in this report provide the best available measure of the national economic burden due to the respiratory diseases studied by this Task Force. In general, the costs are more likely to be understated than exaggerated.

In aggregate, the economic costs in the United States in 1967 from these respiratory diseases was *6.3 billion dollars* (Table 1). This figure includes *$1.7 billion for direct costs of illness*, of which almost $1 billion was for hospital care; *$1.4 billion in indirect morbidity costs* representing approximately *181,000 man-years lost from work* or keeping house by members of the labor force, persons unable to work and housewives; and *$3.2 billion in indirect mortality costs* representing the present value of the remaining earnings of the *126,102 persons who died* due to these respiratory diseases in 1967.

Given the increasing prevalence of some of these diseases, the probable under-reporting in the available data and the necessary use of 1967 figures, the total economic costs to the United States today is likely much more than 6.3 billion dollars.

The following sections will detail the estimation of these morbidity and mortality costs (Table 1).

Table 1

Estimated Economic Costs of Morbidity and Mortality, Number of Deaths, and Man-Years Lost Due to Respiratory Diseases, United States, 1967

Disease Category	Costs (millions of dollars) TOTAL	Morbidity Direct	Morbidity Indirect	Mortality	Number of Deaths	Man-Years Lost (thousands)
TOTAL	$6,289	$1,672	$1,370	$3,247	126,102	180.9
Inhalation Diseases*	112	4	71	37	1,640	8.2
Inorganic dusts	40	4	--	36	1,589	--
Noxious gases & organic dusts	1	--	--	1	51	--
Diseases of the Airways	2,714	1,035	888	804	33,385	124.5
Asthma	515	243	125	147	4,137	
Bronchiectasis	67	23	7	37	1,476	.8
Acute bronchitis	347	211	108	28	957	19.4
Bronchitis, chronic & unqualified	690	374	196	120	5,305	32.5
Pulmonary emphysema & bullous disease	1,066	171	452	443	20,873	54.3
Cystic fibrosis	42	13	--	29	637	--
Interstitial Diseases	2,304	532	411	1,361	55,777	48.2
Collagen diseases	82	25	--	57	1,614	--
Diffuse fibrosis	130	25	--	105	4,218	--
Granulomatosis	14	4	--	10	253	--
Bacterial pneumonitis	1,176	272	80	824	37,369	9.7
Mycobacterial pneumonitis	563	63	282	218	6,349	32.6
Mycoplasma pneumonitis	312	132	49	131	5,174	5.9
Mycotic pneumonitis	9	7	--	2	41	--
Viral pneumonitis	18	4	--	14	759	--
Vascular Diseases	1,146	101	--	1,045	35,300	--
Cor pulmonale & pulmonary hypertension	4	--	--	4	176	--
Pulmonary edema	106	32	--	74	2,555	--
Thromboembolism	253	53	--	200	7,569	--
Hyaline membrane disease	783	16	--	767	25,000	--

*Separate estimates of indirect mortality costs for the two diseases in this category are not possible

MORBIDITY COSTS

The cost of illness may be divided into direct and indirect costs. Direct costs represent expenditures for prevention, detection, treatment, rehabilitation, research, training and capital investments in medical facilities. Indirect costs of illness represent lost earnings as a consequence of illness or disability.

Direct Costs

Estimates of direct costs by type of expenditure for respiratory diseases in 1967 are shown in Table 2. Data for most but not all of the respiratory diseases is available to estimate expenditures for the following: 1) hospital care, 2) physician services, drugs, and nursing home care. These expenditures totaled almost $1.7 billion in 1967. This figure for direct costs of respiratory diseases should be viewed (Table 2) as most conservative because of the lack of data for some of the above categories and for the absence of direct cost information related to research, training, medical facilities construction, and other non-personal services for respiratory diseases.

The procedures used in estimating the expenditures for hospital care, physician services, drugs, and nursing home care are explained in the following sections:

Hospital Care

Care of respiratory disease patients in short-term hospitals cost an estimated $917 million in 1967, representing 11.6 million days of care. Table 2A shows the distribution and costs by specific respiratory disease of these 11.6 million days of hospital care. Except for hyaline membrane disease and cystic fibrosis, hospital outlays by disease were estimated from unpublished provisional data from the Hospital Discharge Survey provided by the National Center for Health Statistics (4).

The Hospital Discharge Survey is a continuing probability sample of all short-term hospitals in the nation excluding military and Veterans Administration hospitals and hospital units of institutions. Short-term means under 30 days average stay per discharge. Patients are tabulated according to the diagnosis listed first on the summary sheet of the patients' records.

In 1967, there were 235 million hospital days of care for all diseases and 11.6 million hospital days of care related to respiratory diseases coded as the primary diagnosis of hospitalization. This figure does not include the number of hospital days that result from respiratory complications of other diseases that might be the first-listed diagnosis, and thus may underestimate the total number of hospital days related to respiratory disease.

The costs of hospital care for specific respiratory diseases are estimated from Social Security Administration data which provide information on national health costs by type of expenditure for all illnesses in aggregate. Data for 1967 are shown in Table 2B.

Table 2

Estimated Direct Costs of Morbidity due to Respiratory Diseases by Type of Expenditure, United States, 1967*

Disease Category	Amount (in millions) Type of Expenditure** Total	Hospital Care	Physicians' Services	Drugs	Nursing Home Care
TOTAL	$1,672	$917	$407	$305	$43
Inhalation Diseases	4	4	---	---	--
Inorganic dusts	4	4	---	---	--
Noxious gases and organic dusts	---	---	---	---	--
Diseases of the Airways	1,035	440	315	237	43
Asthma	243	83	81	61	18
Bronchiectasis	23	13	6	4	--
Acute bronchitis	211	103	61	47	--
Bronchitis, chronic and unqualified	374	148	118	90	18
Pulmonary emphysema and bullous disease	171	87	48	29	
Cystic fibrosis	13	6	1	6	--
Intersititial Diseases	532	401	77	54	--
Collagen diseases	25	18	4	3	--
Diffuse fibrosis	25	16	6	3	--
Granulomatosis	4	2	1	1	--
Bacterial pneumonitis	272	209	36	27	--
Mycobacterial pneumonitis	63	54	6	3	--
Mycoplasma pneumonitis	132	94	22	16	--
Mycotic pneumonitis	7	4	2	1	--
Viral pneumonitis	4	4	--	--	--
Vascular Diseases	101	72	15	14	--
Cor pulmonale and pulmonary hypertension	--	--	--	--	--
Pulmonary edema	32	16	8	8	--
Thromboembolism	53	40	7	6	--
Hyaline membrane disease	16	16	---	--	--

* From Tables 2A, 2C, 2D, 2E

**Excludes expenditures for dentists' services, other professional services, eyeglasses and appliances, prepayment and administration, government and other health services, research and medical facilities construction.

Table 2A

Estimated Number of Days of Hospital Care and Expenditures for Hospital Care due to Respiratory Diseases, Short Stay Hospitals in the United States, 1967*

Disease Category	Number of Days of Care (in thousands)	Expenditures for Hospital Care (in millions)
TOTAL	11,615	$917
Inhalation Diseases	54	4
Inorganic dusts	54	4
Noxious gases and organic dusts	--	--
Diseases of the Airways	5,628	440
Asthma	1,078	83
Bronchiectasis	157	13
Acute bronchitis	1,334	103
Bronchitis, chronic and unqualified	1,933	148
Pulmonary emphysema and bullous disease	1,126	87
Cystic fibrosis**	--	6
Interstitial Diseases	5,214	401
Collagen diseases	244	18
Diffuse fibrosis	216	16
Granulomatosis	30	2
Bacterial pneumonitis	2,716	209
Mycobacterial pneumonitis	704	54
Mycoplasma pneumonitis	1,221	94
Mycotic pneumonitis	44	4
Viral pneumonitis	39	4
Vascular Diseases	719	72
Cor pulmonale and pulmonary hypertension	--	--
Pulmonary edema	205	16
Thromboembolism	514	40
Hyaline membrane disease*	--	16

* References 4,5,6,7
**Number of days of care not available

Table 2B

Aggregate National Health Expenditure by Type of Expenditure, United States, 1967*, All Diseases

Type of Expenditure	Amount (in millions)
Total	$50,763
Health Services and supplies	47,054
Hospital care	18,029
Physicians' services	10,287
Drugs and drug sundries	5,652
Nursing home care	1,858
Other professional services	1,158
Dentists' services	3,360
Eyeglasses and appliances	1,609
Prepayment and administration	1,760
Government public health	942
Other health services	2,339
Research and Medical Facilities Construction	3,709
Research	1,703
Construction	2,006

*Reference 5

Assuming that the distribution by diagnosis is similar for hospital care costs (Table 2B) and for hospital days of care (Table 2A), the hospital care costs for each respiratory disease are estimated as follows:

$$\text{Hospital costs (specific respir. disease)} = \frac{\text{Days of care (specific respir. disease)}}{\text{total days of care (all diseases)}} \times \text{hospital care cost (all diseases)}$$

The Hospital Discharge Survey did not contain the number of days of in-patient care for persons with hyaline membrane disease and cystic fibrosis. Therefore, hospital costs for these two diseases were estimated from cost-per-case information.

For hyaline membrane disease, the hospital care costs are estimated at $16 million for 1967 on the basis of cost-per-case and prevalence data. Approximately 50,000 infants are hospitalized with hyaline membrane disease in the United States each year, and the Department of Public Health of the State of California estimated that the mean hospital care cost per case of hyaline membrane disease was $251 in California in 1965 (5). This estimate was based on a sample of 351 infants with hyaline membrane disease, half of whom died. Adjustment of the cost per case in 1965 for the increase in hospital costs between 1965 and 1967 yields a cost per case of $328 in 1967 dollars.

For cystic fibrosis, the hospital care costs are estimated at $6 million for 1967. This figure derives from an estimated prevalence of 12,000 cases and hospital cost per case information from the Yale Cystic Fibrosis Program (6). Their study of 62 children reported a mean hospital care cost per case of $522* during the period from September 1968 to August 1969 (6). This amounts to $461 in 1967 dollars.

Physicians' Services

Expenditures for physicians' services due to respiratory diseases cost patients $406 million in 1967, representing 51 million visits to physicians in private practice by these patients. Table 2C shows the distribution and costs by specific respiratory disease of these 51 million physician visits.

Physician visit estimates are reported by the National Disease and Therapeutic Index on the total number due to respiratory diseases. The National Disease and Therapeutic Index is a service of Lea Associates, Inc. of Ambler, Pennsylvania. It is a continuing study of private medical practice in the United States in which data are obtained from a representative

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*This is a mean for all cases and not simply for those who required some hospitalization. Of the 62 children, only 11 were hospitalized in the period during which they were studied.

Table 2C

Estimated Number of Physician Visits and Expenditures for for Physicians' Services due to Respiratory Diseases, United States, 1967*

Disease Category	Number of Physician visits (in thousands)	Expenditures for Physicians' services (in millions)
TOTAL	51,071	$406
Inhalation Diseases	--	--
Inorganic dusts	--	--
Noxious gasses and organic dusts	--	--
Diseases of the Airways	39,462	315
Asthma	10,181	81
Bronchiectasis	793	6
Acute bronchitis	7,621	61
Bronchitis, chronic and unqualified	14,771	118
Pulmonary emphysema and bullous disease	6,096	48
Cystic fibrosis**	--	1
Interstitial Diseases	9,646	77
Collagen diseases	526	4
Diffuse dibrosis	795	6
Granulomatosis	168	1
Bacterial pneumonitis	4,438	36
Mycobacterial pneumonitis	747	6
Mycoplasma pneumonitis	2,722	22
Mycotic pneumonitis	250	2
Viral pneumonitis	--	--
Vascular Diseases	1,963	15
Cor pulmonale and pulmonary hypertension	--	--
Pulmonary edema	1,003	8
Thromboembolism	960	7
Hyaline membrane disease	--	--

* References 5,7,8
**Number of physician visits not available

sample of physicians who report case history information on private patients seen over a period of time. While data is lacking for some of the diseases studied by the Task Force, and does not include hospital physicians (emergency room) or public clinic physicians visits, the overall figures do provide a useful but conservative estimate of physician visits related to respiratory diseases.

The costs of physician visits for specific respiratory diseases were estimated from Social Security Administration data on the national health costs for physician visits for all illnesses in aggregate shown in Table 2B. Assuming that the distribution by diagnosis is similar for physician visits (Table 2C) and for physician visit costs (Table 2B), the expenditures for physician visits for each respiratory disease are estimated as follows:

$$\text{Cost of M.D. visits (specific respir. disease)} = \frac{\text{Number of M.D. visits (specific respir. disease)}}{\text{Total M.D. visits (all diseases)}} \times \text{Cost of M.D. Visits (all diseases)}$$

Physician visits for cystic fibrosis were not reported by the National Disease and Therapeutic Index, but the study of the Yale Cystic Fibrosis Program reported a mean cost per case of physician visits of $74 in 1968-69 or $70 in 1967 dollars (7). With a prevalence of 12,000 cases, the total cost of physician visits for cystic fibrosis is estimated at $1 million for 1967.

Drugs

Table 2D presents the estimated costs for drugs prescribed to respiratory disease patients during their more than 46 million physican visits in 1967. Expenditures for drugs related to respiratory disease totaled $305 million in that year.

The National Disease and Therapeutic Index reports patient visits to physicians according to whether or not medication was prescribed (8). While the actual cost of medications for each respiratory disease is not available, an estimate was made from knowledge of the national cost of medications for all illnesses in aggregate (Table 2B), the total number of physician visits with medications prescribed (all illnesses, 886 million), and the number of physician visits for respiratory diseases.

Assuming that the distribution by diagnosis is similar for medication costs (Table 2B) and for patient visits when medication was prescribed (Table 2D), then the expenditures for drugs for each respiratory disease are estimated as follows:

$$\text{Cost of Drugs (specific respir. disease)} = \frac{\text{No. of M.D. Visits with drugs prescribed (specific respir. disease)}}{\text{Total M.D. visits with drugs prescribed (all diseases)}} \times \text{Cost of drugs (all diseases)}$$

Table 2D

Estimated Number of Physician visits for which Drugs were Prescribed and Expenditures for Drugs due to Respiratory Diseases, United States, 1967*

Disease Category	Number of Physician visits (in thousands)	Expenditures for Drugs (in millions)
TOTAL	46,457	$305
Inhalation Diseases	--	--
Inorganic dusts	--	--
Noxious gases and organic dusts	--	--
Diseases of the Airways	36,276	237
Asthma	9,545	61
Bronchiectasis	626	4
Acute bronchitis	7,447	47
Bronchitis, chronic and unqualified	14,149	90
Pulmonary emphysema and bullous disease	4,509	29
Cystic fibrosis**	--	6
Interstitial Diseases	8,358	54
Collagen diseases	403	3
Diffuse fibrosis	564	3
Granulomatosis	90	1
Bacterial pneumonitis	4,146	27
Mycobacterial pneumonitis	474	3
Mycoplasma pneumonitis	2,560	16
Mycotic pneumonitis	121	1
Viral pneumonitis	--	--
Vascular Diseases	1,823	14
Cor pulmonale and pulmonary hypertension	--	--
Pulmonary edema	963	8
Thromboembolism	860	6
Hyaline membrane disease	--	--

*References 5,7,8
**Number of physician visits not available

Table 2E

Estimated Number of Chronic Conditions Reported Among Residents of Nursing and Personal Care Homes and Expenditures for Nursing Home Care due to Diseases of the Airways, United States, 1967*

Disease Category	Number of Conditions	Expenditures for Nursing Home Care (in millions)
TOTAL	38,725	$43
Asthma	16,454	18
Bronchitis, chronic and unqualified**	16,259	18
Pulmonary emphysema and bullous disease	6,012	7

* References 5,9

**In the original data, chronic conditions due to bronchitis and emphysema were combined into a single category. Separate estimates for each condition were made by assuming that the fraction of conditions due to bronchitis, for example, was equal to the number of hospital discharges due to bronchitis divided by the number of discharges due to bronchitis and emphysema.

For cystic fibrosis, the Yale study reported a mean cost per case of $530 for medications in 1968-1969 or $529 in 1967 (7). In terms of all cases of cystic fibrosis (12,000), medication expenses were approximately $6 million.

Nursing Home Care

The National Center for Health Statistics provides data on the number of selected chronic conditions observed among residents of nursing and personal care homes (9). The data is very incomplete for respiratory diseases with only three chronic respiratory conditions reported: 1) asthma; 2) bronchitis, chronic and unqualified; and 3) pulmonary emphysema and bullous disease. In 1967, the chronic care expenditure for these three diseases was $43 million, a figure which represents only a fraction of all respiratory diseases.

The cost of chronic care for these three respiratory illnesses was estimated from knowledge of the number of chronic conditions for each respiratory disease (Table 2E), the total number of chronic conditions in nursing homes (1.7 million), and the estimated total expenditures for all nursing home care (Table 2B). The distribution of these expenditures among the three reported chronic respiratory diseases is shown in Table 2E.

Indirect Costs

Productivity loss because of illness and disability from respiratory diseases cost the nation $1.4 billion in 1967 (Table 3). These losses are measured in terms of days of work lost (expressed as man-years) and the economic value of the associated lost earnings. The estimated losses are given below for three population groups: 1) persons currently employed in the labor force, 2) housewives, and 3) men unable to work at all. Respiratory illness caused almost 181,000 man-years of work loss in these groups in 1967, but the true magnitude of work and productivity loss is even greater since data is not available to estimate losses for the following: 1) women in the labor force who are unable to work at all and 2) persons who reside in institutions (mental, tuberculosis, etc.) who otherwise would be in the labor force.

Currently Employed Population

Morbidity from respiratory diseases among currently employed persons resulted in 79 thousand man-years of work loss, or $561 million in 1967. Table 3A summarizes work and productivity loss data by respiratory disease for the currently employed population. Data is available for only some of the disease categories studied by the Task Force. Consequently, the totals presented in Table 3A underestimate the true magnitude of the problem for all respiratory diseases.

These data were obtained from the National Center for Health Statistics through its National Health Interview Survey. This is a continuing survey interviewing a representative sample of the nation's civilian, noninstitutionalized population to determine the presence of acute and chronic conditions

Table 3

Estimated Man-Years Lost from Work and Keeping House and Indirect Costs of Morbidity due to Respiratory Diseases, United States, 1967*

Disease Category	Man-Year's Lost** (in thousands)	Indirect Costs (in millions)
TOTAL	180.9	$1,370
Inhalation Diseases***	8.2	71
Inorganic dusts	-	-
Noxious gasses and organic dusts	-	-
Diseases of the Airways	124.5	888
Asthma	17.5	125
Bronchiectasis	.8	7
Acute bronchitis	19.4	108
Bronchitis, chronic and unqualified	32.5	196
Pulmonary emphysema and bullous disease	54.3	452
Cystic fibrosis	-	-
Interstitial Diseases	48.2	411
Collagen diseases	-	-
Diffuse fibrosis	-	-
Granulomatosis	-	-
Bacterial pneumonitis	9.7	80
Mycobacterial pneumonitis	32.6	282
Mycoplasma pneumonitis	5.9	49
Mycotic pneumonitis	-	-
Viral pneumonitis	-	-
Vascular Diseases	-	-
Cor pulmonale and pulmonary hypertension	-	-
Pulmonary edema	-	-
Thromboembolism	-	-
Hyaline membrane disease	-	-

* From Tables 3A, 18, 19

**Includes losses by currently employed persons, housewives, and men unable to work

***Not possible to make separate estimates for the two diseases in this category.

Table 3A

Estimated Man-Years Lost from Work and Lost Earnings Due to Respiratory Illness, Currently Employed Persons, United States, 1967*

Disease	Age and Sex	Work Loss Days (Thousands)	Man-Years Lost (Thousands)	Annual Mean Earnings (Dollars)	Lost Earnings (Millions)
TOTAL (all diseases)		19,388	79.1	--	$561
Asthma	Total	4,288	17.5	--	125
	Men 45-64	1,357	5.5	8,947	49.6
Acute Bronchitis	Total	3,632	14.8	--	92.6
	Men, all ages	1,613	6.6	8,015	52.7
	Women, all ages	2,019	8.2	4,835	39.8
Chronic bronchitis	Total	5,141	21.0	--	143.8
	Men 45-64	1,577	6.4	8,947	57.6
	Women 17-44	1,160	4.7	4,631	21.9
	45-64	1,011	4.1	5,223	21.6
Pulmonary Emphysema and Bullous Disease	Total	2,497	10.2	6,904	70.4
Pneumonia**	Total, all men	3,830	15.6	--	129.4
	Men 17-44	1,945	7.9	7,638	60.6
	45-64	1,885	7.7	8,947	68.8

* References 1,10

**Data pertains to bacterial, mycoplasma, and other unspecified pneumonitis. Data for women not available

and the number of days of disability from those conditions. Data on the number of days lost from work because of respiratory illness were provided for the 12-month period ending June 30, 1967 (10).

In Table 3A, age and sex distribution data is presented where available. Work-loss days are expressed as man-years (work-loss days divided by 245, the approximate number of working days in a year) to obtain the indirect costs for the currently employed populations prevented from working due to respiratory diseases.

In Table 16, the average annual earnings (wages and salaries before deductions) were obtained for full-time, year-round, civilian workers (1). Average earnings for persons 14 to 44 years of age are assumed to be approximately the same as for individuals age 17 to 44. Where age-sex distribution data was not available, lost earnings were calculated from the total workdays lost and a weighted average of the earnings for the respective aggregate age group.

Housewives Services

Morbidity from acute and chronic bronchitis among housewives resulted in 14 thousand man-years lost from housework or $45 million in 1967 (Table 3B). Because of data limitations, housewives' services estimates are not available for any other respiratory diseases studied by the Task Force. Therefore, the total amount of $45 million must be viewed as a very conservative estimate.

Housewives' services are estimated at the average earnings of a domestic worker. This imputed value is clearly on the low side, for it make no allowance for the housewife's longer work week and takes no account of the size of the household care for. Although the economic contributions of housewives are not included in the national income accounts, omitting the value of their services in the calculation of indirect costs distorts comparisons of costs among illnesses with different distributions by sex (1).

Information for Table 3B was obtained from unpublished data of the National Health Interview Survey (10). Their data provide the estimated number of disability days in bed for women, a figure which combines homemaker disability and the disability of women in the labor force. Unpublished data on disability days among working women is also available (9) and allows the calculation of disability days for housewives as follows:

Total disability days in bed (all women)	-	days lost from work (working women)	=	disability days (nonworking women)

In order to calculate the economic value of housewife disability due to respiratory disease, the days figure can be converted to work years lost and adjusted for the percent of women not in the labor force who actually keep house (Table 17). The lost income is assumed to be the average wage of a domestic worker, which is $3,281 per year (1).

Table 3B

Estimated Man-Years Lost from Keeping House and Inputed Value of Lost Earnings Due to Illness, Women not in the Labor Force who Keep House, United States 1967*

	Age	Bed Disability Days** (total)	Work Loss Days**	Bed Disability Days** (Housewives)	Percent Keeping House	Man-Years Lost**	Imputed Value of Lost Earnings**
TOTAL		9,828	4,190	5,638	--	13.6	$44.6
Acute Bronchitis	**	3,921	2,019	1,902	89	4.6	15.1
Chronic Bronchitis	17-44	3,526	1,160	2,366	83.7	5.4	17.7
	45-64	2,381	1,011	1,370	95.8	3.6	11.8

* References 1, 10
** All numbers in thousands
***No age distribution available

Table 3C

Estimated Number of Men Unable to Work, Man-Years Lost from Work and Lost Earnings Due to Respiratory Illness, United States, 1967*

Disease	Age	Number Unable to Work (Thousands)	Man-Years Lost (Thousands)	Mean Earnings 1967	Lost Earnings (millions)
TOTAL (all diseases)	--	100.9	88.2	--	$764
Inhalation Diseases*		9.5	8.2	--	71.1
	25-34	0.0	0.0	8,077	0.0
	35-44	0.2	0.2	9,432	1.9
	45-54	2.4	2.3	9,344	21.5
	55-64	6.9	5.7	8,363	47.7
Bronchiectasis		0.9	0.8	--	7.1
	25-34	0.0	0.0	8,077	0.0
	35-44	0.1	0.1	9,432	.9
	45-54	0.3	0.3	9,344	2.8
	55-64	0.5	0.4	8,363	3.4
Bronchitis (chronic & unqualified)		2.8	2.5	--	21.9
	25-34	0.1	0.1	8,077	.8
	35-44	0.2	0.2	9,432	1.9
	45-54	0.8	0.8	9,344	7.5
	55-64	1.7	1.4	8,363	11.7
Pulmonary Emphysema & Bullous Disease		51.5	44.1	--	381.8
	25-34	0.2	0.2	8,077	1.6
	35-44	2.0	2.0	9,433	18.9
	45-54	11.9	11.1	9,344	103.7
	55-64	37.4	30.8	8,363	257.6
Mycobacterial Pneumonitis		36.2	32.6	--	282.1
	25-34	3.0	2.8	8,077	22.6
	35-44	7.4	7.1	9,433	67
	45-54	13.1	12.2	9,344	104.7
	55-64	12.7	10.5	8,363	87.8

* References 1, 11, 12

**Data pertain to pneumoconiosis of occupational origin.

Men Unable to Work

Table 3C summarizes data on morbidity from respiratory diseases among men unable to work at all. Data is available for only some of the diseases studied by the Task Force, so that the total figures do not reflect the true magnitude of the problem for all respiratory diseases.

In 1967, 100,900 men were totally disabled due to the following respiratory diseases: 1) inhalation diseases (pneumoconiosis of occupational origin); 2) bronchiectasis; 3) bronchitis, chronic and unqualified; 4) pulmonary emphysema and bullous disease; and 5) mycobacterial pneumonitis. The disability among men unable to work due to these diseases represents *88,200 man-years lost and $764 million in earnings lost.*

These data were obtained from the Social Security Administration which provides data on the number of men under age 65 unable to work due to respiratory diseases (11). To be included in the data, men had to have been granted disability insurance benefit awards from the Social Security Administration during the years 1959 to 1962. Therefore, these estimates simply give a rough approximation of the number of men under age 65 who were unable to work due to respiratory diseases in 1967.

In Table 3C male labor force participation rates and age-specific unemployment rates for 1967 (from Table 18) were used to estimate man-years lost from work as a result of total disability due to respiratory disease (1). Mean annual earnings for males, by age, were then applied to the man-years lost to obtain indirect costs of morbidity for men disabled due to respiratory diseases.

MORTALITY

The indirect cost of mortality is measured in terms of the discounted present value of lifetime earnings of persons who died (1). *In 1967, the more than 126,000 deaths from respiratory disease represented an estimated indirect cost to the nation of $3.2 billion.* Table 4 summarizes data on mortality and associated indirect cost by disease.

Data for Table 4 were obtained from mortality information published by the National Center for Health Statistics (3), and from unpublished discounted life-time earnings information (Table 19) (1). Mortality information by sex for five-year age groups was available for most respiratory diseases but not for the following: inhalation diseases (inorganic dusts, organic dusts, noxious gases), collagen diseases, granulomatous diseases, viral pneumonitis, mycotic pneumonitis, cor pulmonale, pulmonary hypertension, pulmonary edema, and pulmonary thromboembolism. For these diseases only total mortality estimates and sex distribution data were available. Indirect costs for these diseases were estimated by assuming the age-sex distribution to be similar to related disease groups. For example, deaths by age and sex due to viral pneumonitis were estimated by assuming that sex-specific ratios of total

deaths from viral pneumonia to total deaths from influenza were the same at all ages.

Table 4A summarizes indirect cost, mortality, and sex distribution data for most diseases where complete age information was not available.

Tables 5-15 summarize mortality and economic cost data for the respiratory diseases for which age specific mortality was available. Data on hyaline membrane disease mortality (Table 15) was obtained from the Department of Public Health of the State of California(6), but all other mortality information was provided by the National Center for Health Statistics (3).

Table 4

Number of Deaths and Estimated Indirect Costs of Mortality due to Respiratory Diseases, United States, 1967*

Disease Category	Number of Deaths	Indirect Costs** (in millions)
TOTAL	126,102	$3,247
Inhalation Diseases	1,640	37
Inorganic dusts	1,589	36
Noxious gases & organic dusts	51	1
Diseases of the Airways	33,385	804
Asthma	4,137	147
Bronchiectases	1,476	37
Acute bronchitis	957	28
Bronchitis, chronic & unqualified	5,305	120
Pulmonary emphysema & bullous disease	20,873	443
Cystic fibrosis	637	29
Interstitial Diseases	55,777	1,361
Collagen diseases	1,614	57
Diffuse fibrosis	4,218	105
Granulomatosis	253	10
Bacterial pneumonitis	37,369	824
Mycobacterial pneumonitis	6,349	218
Mycoplasma pneumonitis	5,174	131
Mycotic pneumonitis	41	2
Viral pneumonitis	759	14
Vascular Diseases	35,300	1,045
Cor pulmonale & pulmonary hypertension	176	4
Pulmonary edema	2,555	74
Thromboembolism	7,569	200
Hyaline membrane disease	25,000	767

* From Tables 4A, 5-16
**Present value of lifetime earnings (discounted at 6%) of persons who died from respiratory diseases

Table 4A

Number of Deaths and Estimated Indirect Costs of Mortality
Selected Respiratory Diseases, United States, 1967*

Diseases	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Inhalation Diseases						
Inorganic Dusts	1,589	1,578	11	$ 35,554	$ 35,363	$ 191
Noxious gases & organic dusts	51	46	5	1,103	1,015	88
Interstitial Diseases						
Collagen diseases	1,641	633	981	57,286	23,199	34,087
Granulomatosis	253	99	154	10,085	4,953	5,132
Viral pneumonitis	759	323	436	13,765	7,127	6,629
Mycotic pneumonitis	41	18	23	1,556	842	714
Vascular Diseases						
Cor pulmonale and pulmonary hypertension	176	75	101	4,176	2,038	2,138
Pulmonary edema	2,555	1,475	1,080	73,672	44,576	29,096
Pulmonary thromboembolism	7,569	3,960	3,609	199,538	109,221	90,317

* References 1,3
**Age distribution not available

Table 5

Number of Deaths and Estimated Inidirect Costs of Mortality due to Asthma, United States, 1967*

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	4,137	2,286	1,851	$147,186	$81,469	$65,717
<1	19	11	8	561	387	174
1-4	48	18	30	1,465	723	742
5-9	40	14	26	1,617	755	862
10-14	52	33	19	3,230	2,385	845
15-19	64	28	36	4,607	2,616	1,991
20-24	59	26	33	4,884	2,893	1,991
25-29	67	18	49	5,094	2,136	2,958
30-34	82	36	46	6,933	4,200	2,733
35-39	154	60	94	11,936	6,549	5,387
40-44	190	71	119	13,366	6,869	6,470
45-49	259	100	159	16,067	8,125	7,942
50-54	373	185	188	20,197	11,819	8,378
55-59	438	261	177	19,069	12,178	6,891
60-64	513	315	198	15,041	8,644	6,397
65-69	489	296	193	9,189	4,132	5,057
70-74	511	326	185	7,740	3,791	3,949
75-79	411	271	140	4,610	2,412	2,198
80-84	225	149	76	1,418	770	648
85+	143	68	75	162	58	104

*References 1,3

Table 6

Number of Deaths and Estimated Indirect Costs of Mortality due to Bronchiectasis, United States, 1967*

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	1,476	938	538	$36,925	$23,118	$13,807
1	1	0	1	22	0	22
1-4	2	2	0	80	80	0
5-9	4	3	1	195	162	33
10-14	6	2	4	323	145	178
15-19	9	4	5	650	374	276
20-24	5	5	0	556	556	0
25-29	11	6	5	1,014	712	302
30-34	10	3	7	766	350	416
35-39	23	12	11	1,940	1,310	630
40-44	42	23	19	3,267	2,234	1,033
45-49	60	32	28	3,999	2,600	1,399
50-54	72	44	28	4,059	2,811	1,248
55-59	102	65	37	4,473	3,033	1,440
60-64	160	110	50	4,634	3,019	1,615
65-69	194	128	66	3,516	1,787	1,729
70-74	259	178	81	3,799	2,070	1,729
75-79	213	139	74	2,399	1,237	1,162
80-84	172	112	60	1,090	579	511
85+	131	70	61	143	59	84

*References 1,3

Table 7

Number of Deaths and Estimated Indirect Costs due to Acute Bronchitis
United States, 1967*

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	957	556	401	28,093	18,772	9,321
<1	176	108	68	4,273	3,273	1,477
1-4	132	72	60	4,374	2,891	1,483
5-9	22	10	12	937	539	398
10-14	13	8	5	800	578	222
15-19	16	8	8	1,190	748	442
20-24	8	6	2	789	668	121
25-29	5	4	1	535	475	60
30-34	7	3	4	588	350	238
35-39	19	7	12	1,452	764	688
40-44	20	12	8	1,601	1,166	435
45-49	21	17	4	1,581	1,381	200
50-54	26	15	11	1,448	958	490
55-59	51	35	16	2,256	1,633	623
60-64	54	34	20	1,579	933	646
64-69	67	48	19	1,168	670	498
70-74	76	55	21	1,088	640	448
75-79	72	41	31	852	365	487
80-84	68	36	32	459	186	273
85+	104	37	67	123	31	92

*References 1,3

Table 8

Number of Deaths and Estimated Indirect Costs of Mortality due to Bronchitis, Chronic and Unqualified, United States, 1967*

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	5,305	4,041	1,264	$119,987	$89,214	$30,773
<1	138	89	49	4,192	3,128	1,064
1-4	82	49	33	2,783	1,967	816
5-9	17	7	10	709	377	332
10-14	12	8	4	756	578	178
15-19	13	5	8	909	467	442
20-24	9	8	1	950	890	60
25-29	16	6	10	1,316	712	604
30-34	17	9	8	1,525	1,050	475
34-39	29	19	10	2,647	2,074	573
40-44	72	40	32	5,625	3,885	1,740
45-49	142	100	42	10,223	8,125	2,098
50-54	247	176	71	14,408	11,244	3,164
55-59	425	327	98	19,072	15,257	3,815
60-64	636	505	131	18,090	13,858	4,232
65-69	779	619	160	15,834	8,641	4,193
70-74	892	746	146	11,791	8,674	3,117
75-79	821	660	161	8,402	5,875	2,527
80-84	559	427	132	3,333	2,208	1,125
85+	399	241	158	422	204	218

*References 1,3

Table 9

Number of Deaths and Estimated Indirect Costs of Mortality due to Bullous Disease and Pulmonary Emphysema, United States, 1967*

	Number of Deaths			Indirect Costs (in thousands)		
Age	Total	Male	Female	Total	Male	Female
Total	20,873	17,919	2,954	$442,704	$368,847	$73,857
<1	38	22	16	1,121	773	348
1-4	4	2	2	129	80	49
5-9	3	2	1	141	108	33
10-14	3	2	1	189	145	44
15-19	7	3	4	501	280	221
20-24	5	5	0	556	556	0
25-29	12	7	5	1,133	831	302
30-34	29	17	12	2,696	1,983	713
35-39	70	45	25	6,345	4,912	1,433
40-44	189	143	46	16,390	13,889	2,501
45-49	461	339	122	33,636	27,542	6,094
50-54	957	769	188	57,507	49,128	8,379
55-59	1,839	1,562	277	83,665	72,881	10,784
60-64	2,986	2,585	401	83,891	70,935	12,956
65-69	3,736	3,306	430	57,420	46,152	11,268
70-74	4,129	3,706	423	52,123	43,093	9,030
75-79	3,428	3,003	425	33,405	26,733	6,672
80-84	1,885	1,571	313	10,789	8,122	2,667
85+	1,093	830	263	1,067	704	363

*References 1,3

Table 10

Number of Deaths and Estimated Indirect Costs of Mortality due to Cystic Fibrosis, United States, 1967*

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	637	324	313	$28,717	$17,957	$10,760
<1	179	107	72	5,325	3,761	1,564
1-4	104	43	61	3,234	1,726	1,508
5-9	141	68	73	6,087	3,666	2,421
10-14	82	42	40	4,814	3,036	1,778
15-19	74	36	38	5,465	3,364	2,101
20-24	30	15	15	2,574	1,669	905
25-29	4	3	1	416	356	60
30-34	1	0	1	59	0	59
35-39	2	1	1	166	109	57
40-44	2	1	1	151	97	54
45-49	1	0	1	50	0	50
50-54	1	0	1	45	0	45
55-59	2	1	1	86	47	39
60-64	3	3	0	82	82	0
65-69	2	1	1	40	14	26
70-74	2	1	1	33	12	21
75-79	6	2	4	81	18	63
80-84	1	0	1	9	0	9
85+	0	0	0	0	0	0

*References 1,3

Table 11

Number of Deaths and Estimated Indirect Costs of Mortality due to Diffuse Fibrosis, United States, 1967*

	Number of Deaths			Indirect Costs (in thousands)		
Age	Total	Male	Female	Total	Male	Female
Total	4,218	2,745	1,473	$104,998	$68,910	$36,088
<1	981	554	427	28,749	19,474	9,275
1-4	86	48	38	2,866	1,927	939
5-9	19	10	9	837	539	298
10-14	17	9	8	1,007	651	356
15-19	19	8	11	1,356	748	608
20-24	8	4	4	686	445	241
25-29	14	9	5	1,370	1,068	302
30-34	13	3	10	944	350	594
35-39	24	15	9	2,153	1,637	516
40-44	50	26	24	3,830	2,525	1,305
45-49	110	68	42	7,623	5,525	2,098
50-54	148	84	64	8,218	5,366	2,852
55-59	246	153	93	10,760	7,139	3,621
60-64	360	263	97	10,351	7,217	3,134
65-69	481	359	122	8,209	5,012	3,197
70-74	557	410	147	7,905	4,767	3,138
75-79	531	366	165	5,848	3,258	2,590
80-84	327	222	105	2,043	1,148	895
85+	227	134	93	243	114	129

*References 1,3

Table 12

Number of Deaths and Estimated Indirect Costs of Mortality due to Bacterial Infectious Pneumonitis, United States, 1967*

Age	Number of Deaths			Indirect Costs (in thousands)		
	Total	Male	Female	Total	Male	Female
Total	37,369	21,281	16,088	$824,365	$533,653	$290,712
<1	2,609	1,465	1,144	76,348	51,498	24,850
1-4	818	471	347	27,488	18,909	8,579
5-9	268	143	125	11,855	7,709	4,146
10-14	202	107	95	11,957	7,734	4,223
15-19	251	153	98	19,716	14,297	5,419
20-24	247	142	105	22,135	15,800	6,335
25-29	212	122	90	19,912	14,478	5,434
30-34	311	161	150	27,697	18,785	8,912
35-39	481	280	201	42,080	30,561	11,519
40-44	764	494	270	62,659	47,980	14,679
45-49	1,033	692	341	73,255	56,222	17,033
50-54	1,324	904	420	76,471	57,753	18,718
55-59	1,639	1,125	514	72,502	52,491	20,011
60-64	2,049	1,383	666	59,468	37,951	21,517
65-69	2,752	1,812	940	49,928	25,296	24,632
70-74	4,177	2,700	1,477	62,927	31,396	31,531
75-79	5,232	3,082	2,150	61,187	27,436	33,751
80-84	5,605	2,830	2,775	38,277	14,631	23,646
85+	7,395	3,215	4,180	8,503	2,726	5,777

*References 1,3

Table 13

Number of Deaths and Estimated Indirect Costs of Mortality Due to Mycobacterial Infectious Pneumonitis, United States, 1967*

	Number of Deaths*			Indirect Costs (in thousands)		
Age	Total	Male	Female	Total	Male	Female
Total	6,349	4,683	1,666	$217,692	$164,965	$52,727
<1	8	5	3	241	176	65
1-4	10	5	5	325	201	124
5-9	4	2	2	174	108	66
10-14	7	1	6	339	72	267
15-19	9	3	6	612	280	332
20-24	25	13	12	2,170	1,446	724
25-29	43	21	22	3,820	2,492	1,328
30-34	104	65	39	9,901	7,584	2,317
35-39	215	134	81	19,268	14,626	4,642
40-44	315	203	112	25,805	19,716	6,089
45-49	449	314	135	32,254	25,511	6,743
50-54	592	441	151	34,904	28,174	6,730
55-59	710	545	165	31,853	25,429	6,424
60-64	749	596	153	21,298	16,355	4,943
65-69	807	647	160	13,225	9,032	4,193
70-74	800	635	165	10,906	7,384	3,522
75-79	688	505	183	7,369	4,496	2,873
80-84	465	328	137	2,863	1,696	1,167
85+	349	220	129	365	187	178

*References 1,3

Table 14

Number of Deaths and Estimated Indirect Costs of Mortality Due to Mycoplasma Pneumonitis, United States, 1967*

	Number of Deaths*			Indirect Costs (in thousands)		
Age	Total	Male	Female	Total	Male	Female
Total	5,174	2,907	2,267	$131,430	$85,186	$46,244
<1	1,762	1,053	709	52,416	37,015	15,401
1-4	244	130	114	8,037	5,219	2,818
5-9	43	21	22	1,862	1,132	730
10-14	36	21	15	2,185	1,518	667
15-19	42	19	23	3,047	1,775	1,272
20-24	40	23	17	3,585	2,559	1,026
25-29	35	15	20	2,987	1,780	1,207
30-34	47	27	20	4,338	3,150	1,188
35-39	60	29	31	4,942	3,165	1,777
40-44	62	35	27	4,867	3,399	1,468
45-49	93	53	40	6,304	4,306	1,998
50-54	97	61	36	5,501	3,897	1,604
55-59	149	96	53	6,542	4,479	2,063
60-64	165	102	63	4,834	2,799	2,035
65-69	256	164	92	4,700	2,289	2,411
70-74	354	231	123	5,312	2,686	2,626
75-79	489	282	207	5,759	2,510	3,249
80-84	494	242	252	3,398	1,251	2,147
85+	706	303	403	8.4	257	557

*References 1,3

Table 15

Number of Deaths and Estimated Indirect Costs of Mortality due to Hyaline Membrane Disease, United States, 1967*

Age	Total	Male	Female	Total	Male	Female
Total	25,000	16,675	8,325	$766,996	$586,160	$180,836
<1	25,000	16,675	8,325	766,996	586,160	180,836

*References 1,6

Table 16

Mean Annual Earnings of Men and Women Working Full-time, Year-round, by Broad Age Groups, United States, 1967*

Age and Sex	Number of Persons with Earnings (in thousands)	Mean Earnings, 1967
Men		
14-44	28,660	$7,368
45-64	16,765	8,947
65+	2,058	7,067
Women		
14-44	16,381	4,631
45-64	9,561	4,631
65+	953	4,438

*Reference 1

Table 17

Computation of the Estimated Number of Females in the Noninstitutionalized Population, Not in the Labor Force, Who Keep House, by Broad Age Groups, United States, 1967*

(Number of Thousands)

Age	Number of Females Not in Labor Force	Number Keeping House	Percent Keeping House
17-44	19,362	16,201	83.7%
45-64	10,806	10,353	95.8%
65 & Over	9,243	8,166	88.3%

*Reference 1

Table 18

Labor Force Participation Rates and Unemployment Rates of Men, by Age, United States, 1967*

Age	Labor Force Participation Rate (percent)	Unemployment Rate (percent)
25-34	97.4	2.1
35-44	97.4	1.7
45-54	95.2	1.9
55-64	84.4	2.4

*Reference 12

Table 19

Estimated Present Value of Lifetime Earnings by Age and Sex, United States, 1967*

Age	Men 1967	Women 1967
<1	$35,152	$21,722
1-4	40,147	24,732
5-9	53,909	33,166
10-14	72,283	44,452
15-19	93,443	55,300
20-24	111,267	60,335
25-29	118,677	60,374
30-34	116,675	59,414
35-39	109,148	57,307
40-44	97,125	54,367
45-49	81,246	49,950
50-54	63,886	44,567
55-59	46,659	38,931
60-64	27,441	32,308
65-69	13,960	26,204
70-74	11,628	21,348
75-79	8,902	15,698
80-84	5,170	8,521
85+	848	1,382

*Reference 1

REFERENCES

1. National Heart and Lung Institute Task Force on Arteriosclerosis: Arteriosclerosis. Vol. II, June 1971.

2. World Health Organization: Manual of the International Classification of Diseases, Injuries, and Causes of Death, Vol. I, 1957.

3. National Center for Health Statistics, Division of Vital Statistics: Vital Statistics of the United States, 1967, Vol. II, Part A, 1969.

4. National Center for Health Statistics: Division of Health Resources Statistics, Hospital Discharge Survey Branch; unpublished provisional information obtained by personal communications.

5. Social Security Administration: Research and Statistics Note No. 25, National Health Expenditures, Fiscal Years 1929-70 and Calendar Years 1929-69, December 14, 1970.

6. State of California, Human Relations Agency, Department of Public Health: A Report to the 1971 Legislature on Hyaline Membrane Disease. July 1971.

7. McCollum, A.T.: Cystic Fibrosis: Economic Impact Upon the Family. Amer. J. of Public Health, 61: 1335-1340, 1971.

8. Lea Incorporated: National Disease and Therapeutic Index, Reference File for June 1966 to July 1967.

9. Nelson, A.B.: Prevalence of Chronic Conditions and Impairments Among Residents of Nursing and Personal Care Homes, National Center for Health Statistics, PHS Publication No. 1000, Series 12, No. 8. 1967.

10. National Center for Health Statistics: Division of Health Interview Statistics. Unpublished information obtained by personal communication.

11. Social Security Administration: Occupational Characteristics of Disabled Workers by Disabling Conditions: Disability Insurance Benefit Awards Made in 1959-1962 to Men Under Age 65. Public Health Service Publication No. 1531. 1967.

12. Department of Labor: Manpower Report of the President. 1969.

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